Psychosocial Factors in the Triggering of Acute Coronary Syndromes

PhD Submission

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Strike PC, Steptoe A. New insights into the mechanisms of temporal variation in the incidence of acute coronary syndromes. Clinical Cardiology 2003; 26: 495-499.

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Strike PC, Steptoe A. Behavioural and Emotional Triggers of Acute Coronary Syndromes. Psychosomatic Medicine 2005; 67(2): 179-86

These papers are included at the end of the thesis.

Abstract

There is evidence that emotional and behavioural (psychosocial) factors influence the natural history of coronary artery disease (CAD) and the incidence of acute coronary syndromes (ACS). However there are many inconsistencies in the methodologies and results of existing studies, and carefully controlled data are scarce. This thesis examines the theoretical background and mechanisms by which psychosocial factors influence ACS. The evidence assessing timing and triggering of ACS, mental stress-induced myocardial ischaemia and the role of psychosocial factors in the development of CAD and ACS is examined. This information is used to identify areas in which there is currently a lack of knowledge and generate several hypotheses which are tested in three studies.

Firstly, a prospective, multi-centre cohort study was performed, interviewing ACS patients within 4 days of hospital admission. Case-crossover methodology was used to assess the impact of acute psychosocial factors on ACS triggering. Increased relative risk of ACS following acute mental stress, anger or depression was demonstrated, and these factors interacted with social and temporal factors affecting ACS incidence. Clinical, electrocardiographic and biochemical correlates were also analyzed, and an increased incidence of ST segment elevation and greater release of markers of myocyte necrosis was observed in patients exposed to acute psychosocial triggers.

Secondly a laboratory study was conducted to assess the effects of mental stress upon haemostatic and haemodynamic responses in CAD patients compared with age-matched healthy controls. This demonstrated abnormal blood pressure, peripheral resistance and platelet responses to mental stress in CAD patients.

The third study examined psychobiological reactivity in a sub-set of patients from the first cohort study, assessing correlations between laboratory stress-reactivity, clinical findings and psychosocial exposure at ACS onset. This demonstrated that social deprivation affects haemodynamic and platelet psychobiological reactivity, and that patients with trigger-induced ACS display greater platelet stress-reactivity than controls. The implications of these findings for future research and therapeutic interventions are discussed.

Abbreviations Used

5HT	5 hydroxy-tryptamine
ACCENT	Acute Coronary Syndrome: Emotion and Triggers
ACS	acute coronary syndrome
AMI	acute myocardial infarction
BMI	body mass index
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CBT	cognitive behavioural therapy
CK	creatinine kinase
CO	cardiac output
COi	cardiac output index
CRP	C-reactive protein
ECG	electrocardiograph
ENRICHD	"Enhancing Recovery in Coronary Heart Disease"
ERI	effort-reward imbalance
GRACE	Global Registry of Acute Coronary Events
HADS	Hospital anxiety and depression scale
HR	heart rate
HPA	hypothalamic-pituitary-adrenal axis
ICAM	intercellular adhesion molecule
IL-6	interleukin 6
IVUS	intravascular ultrasound
LP(a)	lipoprotein (a)
LPSS	low perceived social support
LVEF	left ventricular ejection fraction

MA	mental arithematic
MCP	monocyte chemattractant protein
MILIS	Multicenter Investigation of Limitation of Infarct Size
MSIMI	Mental stress-induced myocardial ischaemia
NQWMI	non Q-wave myocardial infarction
NSTEMI	non ST-elevation myocardial infarction
PAI	plasminogen activator inhibitor
PCI	percutaneous coronary intervention
PET	positron emission tomography
PIMI	Psychophysiological Investigations in Myocardial Ischaemia
PLA	platelet leucocyte aggregate
PS	public speaking
QWMI	Q-wave myocardial infarction
RPP	Rate pressure product
RT	reaction time
SADHART	Sertraline AntiDepressant Heart Attack Randomized Trial
SCD	sudden cardiac death
SES	socio-economic status
SHEEP	Stockholm Heart Epidemiology Programme
SSRI	selective serotonin release inhibitor
STEMI	ST-elevation myocardial infarction
SV	Stroke Volume
SVi	Stroke Volume index
TIMI	Thrombolysis in Myocardial Infarction
TIMP	tissue inhibitor of metallo-proteinase
TNF	tumour necrosis factor

TPR	Total peripheral resistance
TRIMM	Triggers and mechanisms of myocardial infarction
UA	unstable angina
WBC	white blood cell
WMA	wall motion abnormality

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Chapter One

INTRODUCTION

1.1 INTRODUCTION

Coronary Artery Disease (CAD) remains one of the biggest causes of death in the Western World despite intense public health efforts over the last forty years. It will soon become the pre-eminent health problem world-wide [1]. In the United Kingdom over 124 000 people died from CAD in the year 2000 [2]. It is a cause of immense morbidity (there are over two and a half million patients with CAD now in the UK) and a huge consumer of financial and healthcare resources with an annual cost of approximately £7 billion to the UK economy.

Traditional risk factors for CAD (diet, physical activity, diabetes mellitus, smoking, high body mass index, hypertension) account for between 58 and 75% of incident cases of CAD [3]. This still leaves a huge amount of mortality and morbidity unaccounted for (up to almost 100 000 deaths in the U.K. in 2000). Consequently the search for other important factors that may influence the disease process, such as psychological, behavioural and social factors (subsequently referred to as psychosocial factors) has occurred with the aim of explaining this discrepancy. Clearly, any intervention or therapeutic manoeuvre which could decrease this burden of illness would potentially have massive public-health benefits.

Interest in psychological factors as triggers of ACS is not new. In the original clinical description of acute myocardial infarction in 1910, Obrastsov and Strazesko noted "Direct events often precipitated the disease; the infarct began in one case on climbing a

high staircase, in another during an unpleasant conversation and in a third during emotional distress associated with a heated card game"[4 5]. The subject was contested over the next 50 years with various proponents for and against the argument [5]. However, subsequent work in the 1960s suggested that "coronary occlusion takes place irrespective of the physical activity being performed or the type of rest taken" [6] and the concept of external events acting as triggers for acute myocardial infarction fell out of favour for many years before interest rekindling in 1985 [5 7]

CAD is a disease process which occurs over many years. To influence atherosclerotic disease progression, psychosocial factors must influence the body's physiological mechanisms to alter biochemical and cellular function. Psychosocial factors may theoretically affect this disease over several different time scales; chronically over many years with factors such as socio-economic class, episodically with conditions such as depression or more acutely in the case of anger and mental stress. The concept of environmental factors influencing such complex factors such as gene expression and cellular behaviour is a fascinating one and identifying the pathways by which psychosocial factors may have this effect is a great challenge, and potentially one with great public health repercussions. Greater understanding of the biochemical, genetic and cellular pathways may lead to the possibility of therapeutic inhibition of some of the detrimental effects of psychosocial factors on the disease process.

The majority of the mortality due to CAD is due to its most common acute manifestation – the acute coronary syndrome (ACS). It is therefore important to attempt to understand the ways in which psychosocial factors may influence both the chronic atherosclerotic disease process and the acute triggering of ACS. Chapter 2 takes an overview of the chronic and acute atherosclerotic processes and how some atherosclerotic plaques may become vulnerable to rupture leading to ACS. Chapter 3 discusses the evidence linking

chronic psychosocial factors (social class, social support, chronic stress, hostility / anger, and depression) with the chronic development of CAD.

The time and pattern of onset of ACS is influenced by many factors and is not randomly distributed. Understanding more about these patterns of incidence may help understanding of the underlying pathophysiology. Incidence is influenced by daily, weekly and annual periodicity as well as by acute environmental, psychological and behavioural factors (such as physical exertion, mental stress and air pollution). These patterns suggest that these acute external influences cause triggering of the ACS via effects on the body's physiology and thus suggest how psychosocial and environmental factors are linked with acute CAD. In Chapter 4 the literature regarding the temporal distribution of ACS is reviewed followed by a review of the role of acute psychosocial triggers and discussion of the underlying mechanisms in Chapter 5. Chapter 6 adds to the examination of triggering mechanisms by systematically reviewing the current available data assessing the role of acute mental stress in the induction of myocardial ischaemia. This may be particularly relevant in cases of ACS which present as sudden cardiac death (SCD).

There is a great individual variation in the development of CAD and we do not know why some people appear to develop CAD and others do not. Similarly we do not know why factors such as low socio-economic status or acute mental stress influence the pathophysiology of cardiovascular disease in some patients but not others. With regard to psychosocial factors, there is an increasing belief that this may be due to a difference in "psychobiological reactivity" i.e. in the way that different individuals mount a physiological response to psychological and environmental stress. Some people may manifest a more exaggerated haemodynamic, physiological and biochemical response to

stress than others. This could result in prolonged or exaggerated injury to the vascular wall, chronically promoting the atherosclerotic process and acutely favouring plaque rupture and subsequent intravascular thrombosis.

Although we are gradually gaining more knowledge about the roles that psychosocial factors may play in the incidence of CAD, There are still several areas which have not previously been adequately investigated.

1. What is the role of acute stress and depression as potential trigger factors for ACS? Are the different forms of ACS affected differently?

Currently the only psychological factor which has been specifically examined in controlled studies in the critical two hour period pre ACS is anger. The effect of acute mental stress and depression in this acute period are not known. Studies of this topic cause a number of important methodological issues which will be addressed in Chapters 5 and 8.

2. How do psychosocial factors influence the clinical presentation and subsequent course of ACS?

We do not know for example if people with acute or chronic stress preceding their ACS have clinical indicators of increased disease severity or poorer prognosis compared to those individuals without stress. There has been no investigation as yet into how these psychosocial factors may influence the clinical presentation of ACS. Clinical factors may influence physical findings (such as pulse or blood pressure) or the results of investigations such as the electrocardiographic findings both acutely and upon ACS resolution and may also influence the results of blood tests such as creatinine kinase or

troponin measurements. Might these clinical criteria give us some idea about the underlying mechanisms of acute disease causation?

3. Does a difference in psychobiological reactivity in people with CAD compared with people without explain part of the disease process and which physiological mechanisms are implicated?

4. Does a difference in psychobiological reactivity explain the development of ACS in those in whom acute stress triggers an ACS compared with controls?

It is unknown whether patients in whom stress triggers an ACS have a difference in haemodynamic, vascular, haemostatic or inflammatory reactivity to stress compared with patients in whom stressful events do not trigger an ACS. There has been no investigation in persons who have sustained acute coronary syndromes to examine their psychobiological reactivity and correlate this with clinical presentation and psychometric variables.

This has led to 4 main objectives in this thesis.

1.2 OBJECTIVES

1. To assess the prevalence of acute psychosocial factors triggering ACS.
2. To examine the association between acute psychosocial triggers and clinical parameters
3. To examine whether patients with CAD have an altered psychobiological reactivity compared with healthy controls.

4. To examine whether patients with ACS triggered by acute psychosocial factors have an altered psychobiological reactivity compared with non-triggered ACS patients.

Chapter 7 lays out the study rationale and methods for the ACCENT (ACute Coronary syndrome: EmotioN and Triggers) study – a prospective cohort study designed to investigate the prevalence of acute psychosocial factors preceding ACS and to correlate the clinical findings at the time of ACS with psychosocial factors. The results of this are presented in Chapter 8. This study involved a collaborative group of researchers , and I will detail my contributions and independent work in Chapter 7.

Chapter 9 describes a laboratory experiment examining the haemodynamic, inflammatory and platelet reactivity of patients with CAD compared with age and sex matched controls. Chapter 10 describes another laboratory experiment investigating the psychobiological reactivity in patients who have recently sustained an ACS.

I have used a novel combination of patient interview, psychometric questionnaires and clinical data to try and find new perspectives and correlations between psychosocial and clinical findings. These areas have not previously been investigated in an integrated way to any significant degree. Previous investigations have either focused on clinical assessments of psychosocial triggers of ACS or on laboratory studies of psychobiological reactivity to mental stress, but have not combined these perspectives.

Chapter Two

PLAQUE BIOLOGY, VULNERABLE PLAQUES AND PATIENTS, AND ACUTE CORONARY SYNDROMES

The fundamental lesion in the pathophysiology of CAD is the atherosclerotic plaque. This lesion is seen as early as childhood in the form of fatty streaks. The most likely model of pathogenesis is that genetic risk factors interact with environmental and chronic psychosocial factors to promote formation of atherosclerotic plaques. Acute risk factors then act upon these plaques to cause acute coronary syndromes. To understand the mechanisms by which psychosocial factors can influence the natural history of CAD and ACS it is necessary to understand the processes involved in atherosclerosis and in the pathogenesis of ACS.

2.1 THE ATHEROSCLEROTIC PROCESS

It is thought that abnormalities of cellular and molecular function combine to promote atherogenesis as an endothelial response to injurious stimuli such as free radicals. The earliest changes that precede the formation of lesions of atherosclerosis take place in the endothelium (figure 2.1.). The normally functioning endothelial monolayer in contact with flowing blood resists firm adhesion of leucocytes and has anticoagulant properties. The compensatory response to injury is to increase the endothelial permeability to platelets and leukocytes, to increase endothelial adhesive and procoagulant properties and to induce the production of cellular messengers stimulating cell migration [8 9]. Stimulated adhesion molecules on the endothelium (such as selectins and intercellular adhesion molecules – ICAMs) act in conjunction with chemoattractant molecules to

initially attract leukocytes onto the endothelial wall and then facilitate movement across the endothelium into the vessel wall itself. Vascular cell adhesion molecule – 1 (VCAM – 1) has a particular affinity for this leucocyte class. Transcription of the VCAM-1 gene occurs in response to inflammatory stimulation by such molecules as modified low density lipoprotein molecules and is mediated by nuclear factor κB [10].

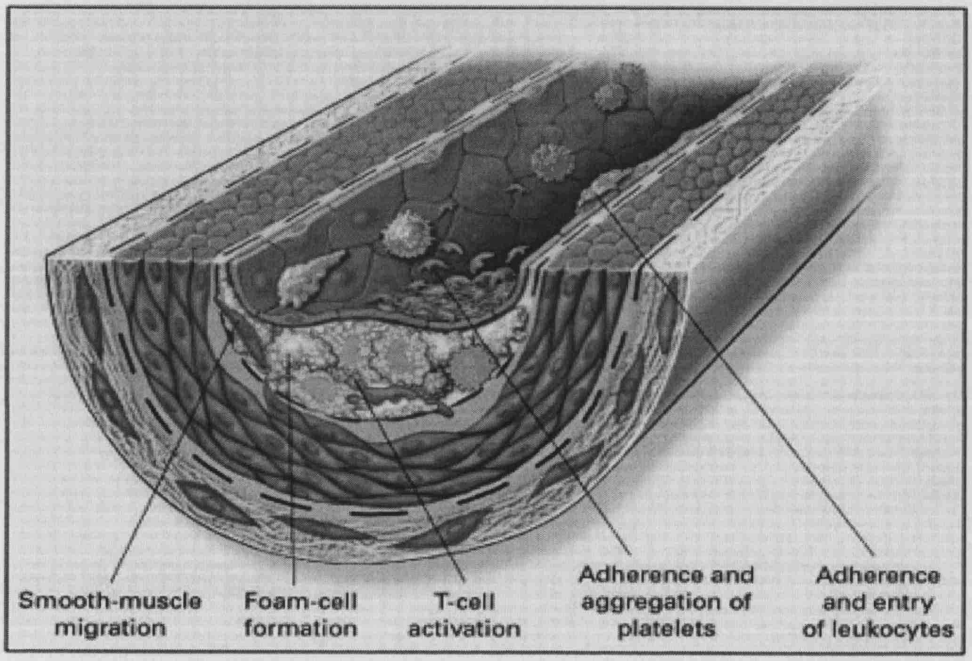


Figure 2.1. Endothelial Dysfunction in Atherosclerosis. *Endothelial changes include increased endothelial permeability to lipoproteins and other plasma constituents, which is mediated by nitric oxide and other chemokines; up-regulation of leukocyte adhesion molecules; up-regulation of endothelial adhesion molecules, and migration of leukocytes into the artery wall.* Taken from Ross R, Atherosclerosis – an Inflammatory Disease [9].

The monocytes diapedese between intact endothelial cells into the tunical intima and become macrophages. They then become laden with lipid, becoming foam cells which

release growth factors and cytokines which amplify the local inflammatory response within the lesion [11]. These cells die in the vessel wall and are attacked by hydrolytic enzymes which cause cellular necrosis and form the necrotic cell and lipid rich cores of the plaque lesions (figure 2.2). A fibrous cap forms over the vascular aspect of the lesion with smooth muscle cells.

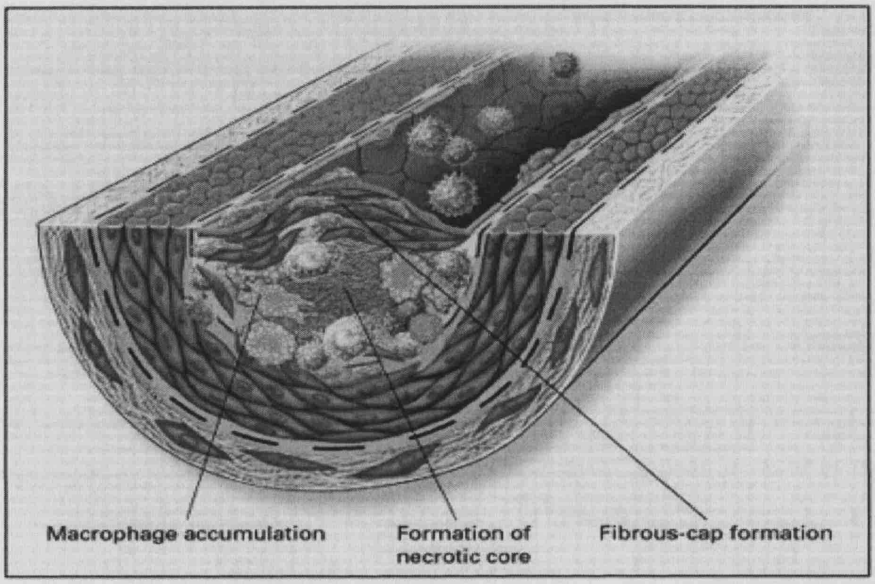


Figure 2.2. Formation of an Advanced Atherosclerotic Lesion. *As advanced lesions form, a fibrous cap walls off the lesion from the lumen. This represents a type of healing or fibrous response to injury. The fibrous cap covers a mixture of leucocytes, lipid, and debris, which form a necrotic core. The necrotic core represents the results of apoptosis and necrosis, increased proteolytic activity, and lipid accumulation.* Taken from Ross R, Atherosclerosis – an Inflammatory Disease [9].

Lesion expansion occurs at the shoulders of the plaque by means of continued leukocyte adhesion and entry [9]. Psychosocial factors might affect the disease process by acting at several points in this chain of events.

Arterial remodeling occurs with a range of responses from constriction of the vessel lumen to compensatory enlargement of the vessel and net movement of tissue away from the lumen[12]. The atherosclerotic plaques remain clinically quiescent until it either intrudes enough into the lumen of the vessel as to become flow limiting (causing exertional angina) or until rupture of the fibrous cap of the plaque occurs leading to contact of the bloodstream with the procoagulant lipid core resulting in intravascular coagulation and an acute coronary syndrome (ACS).

Serial angiographic studies have suggested that plaque progression may not be a smooth, continuous process but that it may occur in bursts of growth [13].It has been suggested that physical disruption of plaques may cause thrombosis and promote sudden expansion of atheromatous lesions[8] [14]. This can happen in three ways by superficial erosion of the surface of the plaque leading to platelet thrombosis on the underlying collagen of the endothelium, intraplaque haemorrhage secondary to rupture of plaque associated neo-vascularisation and plaque rupture. It is possible that psychosocial factors may partially exert their influence on the natural history of coronary artery atherosclerosis by affecting these mechanisms.

2.2 PLAQUE RUPTURE

Plaque rupture occurs when there is a breach in the fibrous cap of the plaque and the contents of the lipid core becomes exposed to the bloodstream (figure 2.3). Plaque rupture is felt to be the underlying pathological event in the initiation of the majority of clinical acute coronary syndromes with thrombus formation due to superficial erosion responsible in about one quarter of cases [8 15 9 16].

The atherosclerotic plaque is not a static entity; it is a dynamic structure in which there is considerable metabolic activity and constant remodeling. Although a balance usually exists between degradation and synthesis allowing plaque stability, the equilibrium between matrix metalloproteinases, cathepsins, tissue inhibitors of metalloproteinases and other plaque enzymes may alter favouring instability. Arteries also express endogenous agonists of matrix metalloproteinases called tissue inhibitors of metalloproteinases (TIMPs). The balance between synthetic and degradative processes is controlled by inflammatory regulators which control among other things the level of collagen in the fibrous cap. Pro-inflammatory cytokines can induce matrix metalloproteinases (altering the equilibrium with TIMPs) and gelatinases and can also trigger apoptosis of smooth muscle cells. Consequently plaque rupture can occur due to intrinsic degradation or to increased external shear stresses or to a combination of the two.

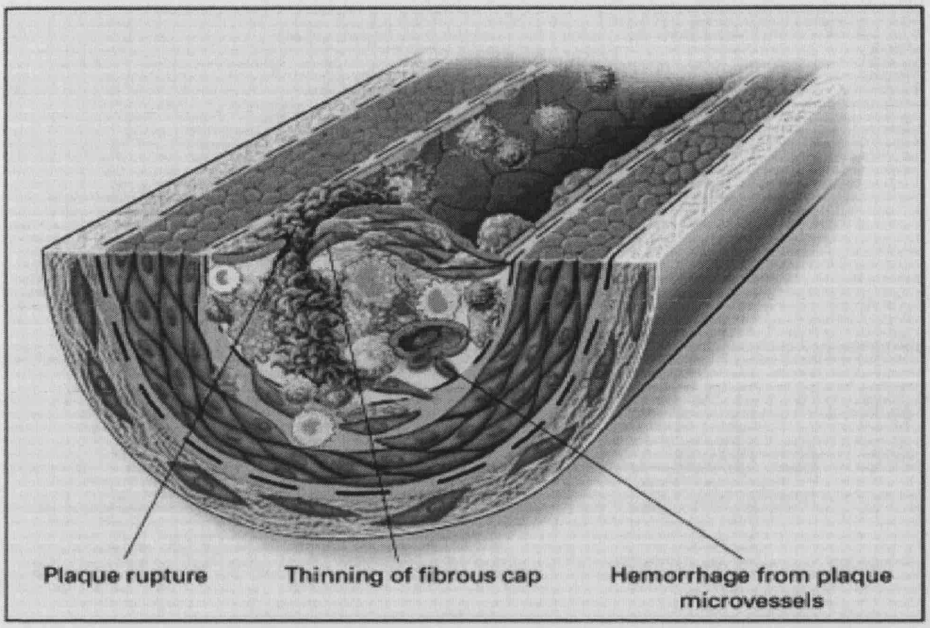


Figure 2.3. Unstable Fibrous Plaques in Atherosclerosis. *Rupture or ulceration of the fibrous plaque usually occurs at sites of thinning. Macrophages, release metalloproteinases and other proteolytic enzymes which cause degradation of the matrix, and can lead to haemorrhage from the vasa vasorum or from the lumen of the artery and can result in thrombus formation and arterial occlusion.* Taken from Ross R, Atherosclerosis – an Inflammatory Disease [9].

2.3 THE ACUTE CORONARY SYNDROME

Rupture may occur in response to haemodynamic stresses or to erosion of the plaque from the vascular aspect or by degradation from within. Plaque rupture may be a clinically silent event [16] or can lead to presentation as an acute coronary syndrome (ACS). The three different ways that an ACS can present are as an acute myocardial infarction (AMI), unstable angina (UA) or sudden cardiac dearth (SCD). These three forms of ACS are all thought be mostly due to plaque rupture and together form the basis for the majority of clinical problems due to coronary atherosclerosis. Sudden cardiac death may differ in aetiology in some cases as myocardial ischaemia or other arrhythmic

substrates may predispose to ventricular dysrhythmia in the absence of plaque rupture or erosion. Without the damage done by ACS, other ischemic problems such as heart failure and dysrhythmias would be far less prevalent.

People who suffer sudden cardiac death due to plaque rupture are not fortunate enough to be seen in hospital and clinically assessed. For the remainder of ACS patients, sub-categorisation of their ACS can be made using presenting electrocardiographic details and biochemical markers of myocyte necrosis (see figure 2.4). ACS are categorized as being ST-elevation myocardial infarctions (STEMI), non-ST-elevation myocardial infarctions (NSTEMI) or unstable angina. The diagnostic categorization of ACS and AMI has recently been redefined by a joint working group from the American College of Cardiology and the European Society of Cardiology [17]. This has been done to incorporate the advent of new highly sensitive serum biomarkers of myocyte necrosis – the troponins [17]. This now allows accurate diagnosis of myocardial infarction based on a troponin value of greater than the 99th percentile of a reference control group. This has led to an increase in the diagnosis of AMI [18] as many cases previously diagnosed as unstable angina are now diagnosed as myocardial infarctions. Myocardial infarctions can also be categorized as to the presence or absence of Q-waves on the final ECG (a broad correlate of the severity of an AMI as the presence of Q waves on an ECG correlates with the incidence of transmural infarction). This used to be the categorization of choice, but more recently the STEMI / NSTEMI nomenclature has come into common usage as these findings have direct impact upon the immediate and early clinical treatment.

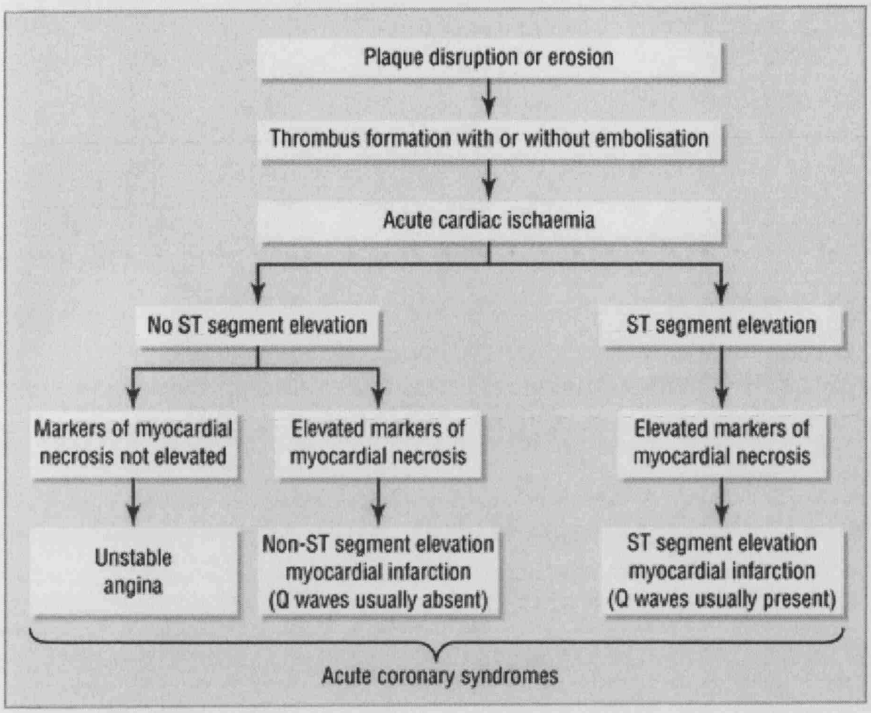


Figure 2.4. The spectrum of acute coronary syndromes according to electrocardiographic and biochemical markers of myocardial necrosis (troponin T, troponin I, and creatine kinase MB), in patients presenting with acute cardiac chest pain. From Grech and Ramsdale [19]

2.4 PATIENT AND PLAQUE VULNERABILITY

One of the most commonly held theories regarding the onset of ACS is that the patient must be in a "vulnerable state" to initially allow the rupture or erosion of an atherosclerotic plaque, and then for this to lead onto a clinically evident syndrome. Initially vulnerability to ACS was just thought of in terms of vulnerable atherosclerotic plaques, i.e. a plaque that through a shift in the equilibrium between synthetic and degradative processes would rupture spontaneously or would rupture with the superadditive effect of an external triggering stimulus. More recently there has been a more holistic shift in emphasis to consideration of the "vulnerable patient" [15 20]. Vulnerability to an ACS reflects an interaction of several factors. The concept of the

vulnerable patient represents a combination of atherosclerotic plaque vulnerability, "vulnerable blood" (a procoagulant state as well as circulating inflammatory molecules and markers of increased risk), and "vulnerable myocardium" (propensity of the myocardium to become dysrhythmic with ischaemic insult) [15 20]. The aspect of the vulnerable myocardium is most likely to be important in those patients who have arrhythmia or SCD as the presentation of their ACS.

The concept of the vulnerable patient as a whole rather than just plaque vulnerability is supported by evidence from autopsy, intravascular ultrasound (IVUS) and neutrophil myeloperoxidase studies which suggest that in at least some cases there may be a "pan coronary" vulnerable state rather than just a single vulnerable plaque [15 20 21]. Rioufol et al found IVUS evidence of ruptured plaques apart from the culprit lesion for ACS in 9/24 patients [21]. However it is most likely that the same determinants of single plaque vulnerability would also contribute in a similar fashion to a pan coronary susceptibility to ACS and so they will be considered in the same way. Plaque vulnerability will be briefly discussed here and then in more detail in Chapter 6 along with the other mechanisms affecting factors such as platelets, haemostatic factors and the autonomic nervous system.

Plaque vulnerability is probably a continuum rather than a dichotomous state of vulnerability or non-vulnerability. Consequently some patients with extremely vulnerable plaques may need only a slight trigger to cause rupture, while in others a greater stimulus is required. Vulnerable plaques are characterized by active inflammation, macrophage accumulation and activated T cells, a thin fibrous cap with a large lipid core, and endothelial denudation with platelet aggregation [22]. At these times of vulnerability, the occurrence of a trigger causing an acute physiological response such as

a rise in blood pressure (causing increased shear stress across the plaque) or an increase in plaque inflammation (leading to increased degradation) could lead to rupture and subsequent ACS. It seems likely that plaques go through cycles of stability and vulnerability, and at any one time there may be plaques in a spectrum of states of vulnerability.

It is conceivable although as yet unproven that environmental factors which promote an inflammatory physiological response may play a part in fostering plaque instability by favouring degradation. Other factors may be important such as production of oxygen free radicals by inflammatory cells which may have a direct destructive effect within the plaque, and intraplaque haemorrhage from the vasa vasorum also contributing to promotion of instability.

Vulnerable plaques can not usually be identified angiographically. The majority of plaques which rupture are not the most angiographically severe, partly due to a process of positive remodeling of the arterial wall. Vulnerability can be assessed by experimental techniques such as angioscopy or thermography catheters but these are not in widespread clinical usage. It is difficult to screen widely and prospectively for the existence of vulnerable plaques although there are some serological markers such as CRP which may give an indication of overall vulnerability. At the moment there is no adequate screening test for vulnerability. Even with the use of composite markers in assessment it is unlikely that in the near future a test will become available because a state of vulnerability is likely to be transient and intermittent.

Clearly the regulation and expression of endothelial adhesion molecules, inflammatory markers and cellular messengers is of key importance in the atherosclerotic process and

maybe even in the more acute setting. The work of Davies et al indicates that plaque rupture appears to be a more common event than the development of ACS [16]and so other factors such as effects on blood platelets and the coagulation system, medications such as aspirin which affect coagulation, or mechanisms which effect coronary artery vascular tone may be important in determining the degree of intravascular coagulation and vessel occlusion and thus ultimately clinical events [540, 22a - d]. Consequently any factors which affect cardiovascular event rates may work via these mechanisms or via mechanisms such as the matrix metalloproteinases (such as stromelysins, elastases and collagenases) which are involved in the degradation of components of the atherosclerotic plaque.

An important consequence of these pathophysiological processes is that triggers could operate in two ways. The first possibility is that triggers cause ACS in patients who would have suffered a cardiac event in the very near future anyway, harvesting highly vulnerable plaques through rupture or erosion. The second possibility is that triggers cause ACS in patients who would otherwise have remained stable, by stimulating the combination of inflammation, procoagulatory responses and autonomic imbalance. In such cases, the trigger may not cause plaque rupture or erosion, but rather affect the milieu in which the rupture takes place, ensuring that it is followed with sufficient thrombosis or ventricular instability to promote a clinical cardiac event.

Chapter Three

THE EVIDENCE FOR PSYCHOSOCIAL FACTORS INFLUENCING THE CHRONIC DEVELOPMENT OF CORONARY ARTERY DISEASE

3.1 INTRODUCTION

Psychosocial factors have a profound effect upon everyone from the time of childhood (or even maybe as early as intra-uterine life) onwards and are likely to affect many parameters of health and wellbeing. We are all exposed to psychosocial influences such as social status and social support throughout our entire lives, and a large number of people spend the majority of their day-time lives in the workplace. Atherosclerosis is a chronic disease process. We know that fatty atherosclerotic streaks have been seen in the arterial walls of children and it is likely that these are preceded by a sub-clinical phase of endothelial dysfunction. It is likely that psychosocial factors play important roles not only in chronic disease initiation and progression of coronary atheroma but also in influencing acute events. They are also likely to have an important role in the clinical and psychological manifestations of acute coronary syndromes as well as recovery and subsequent long-term outlook. Consequently the way in which our psychosocial environment can influence the progression of atherosclerotic disease and its effect on acute coronary events is of great importance.

3.2 CHRONIC PSYCHOSOCIAL FACTORS AND THE DEVELOPMENT OF CORONARY ARTERY DISEASE

There is now a wealth of data looking at the relationship of psychosocial factors to development of CAD, risks for acute coronary syndromes (ACS), and prognosis after coronary syndromes. Five main psychosocial areas have been examined: - acute and chronic stress, depression, socio-economic status, personality traits and social support and their link with development of CAD. This chapter looks at the epidemiological data (concentrating on the epidemiologically most sound studies) for psychosocial factors in the development of CAD. Animal studies are not discussed, even though these provide important evidence for an influence of social disruption and other stresses on atherogenesis [23-25] Chapter 5 then outlines the links between these factors and ACS onset. Many of the factors which are discussed in relation to CAD development are also common to the pathogenesis of acute events and subsequent prognosis. Review of this data has already been published [26] and a general critique of this literature is provided towards the end of this chapter (section 3.10).

3.3 CHRONIC LIFE STRESS

3.3.1 Work Stress

For a large number of adults, a huge part of their waking time is spent in the work environment and many find it a stressful and sometimes unenjoyable experience. Consequently any factors exerting influence here have a great deal of time to have their effect. It has been estimated that 10% - 40% of the workforce suffer from work stress,

and that at least a third of these have severe chronic psychosocial stress [27]. The observation that some occupations (such as drivers) have consistently higher rates of cardiovascular disease has prompted further investigation to identify factors in the working environment that might be detrimental to health. There are however, several difficulties in addressing the question of work stress, for example the close relationship with socio-economic status (SES), amount of social support at home or at work, conventional cardiovascular risk factors, education, and psychological traits.

Assessment of work stress can take place via either self-reporting (using standardized questionnaires) or external assessment of job stress. Obviously self-reporting may be susceptible to bias, although self-reported and independently assessed job control show similar associations with CAD [28]. Other problems with the assessment occur in long-term follow up where the "healthy worker effect" may be seen as more ill or susceptible employees leave work or go to less stressful posts, leaving the healthier people in the study. A wide range of settings have been looked at in different countries and different work situations. However, several studies have also used single occupation groups which might be too narrow a focus to demonstrate links in jobs stresses and health outcomes which may exist in the general population. Finally, the vast majority of work relates to men.

Two main models of work stress have been developed to allow conceptualization of the heterogeneous employment world; these are the Job Strain and the Effort Reward Imbalance Models. The job strain model [29] or the "demand-control" model centres on the concept is that the highest job strain occurs in those workers who have high psychological demands at work but little job control leading to stress. Effort-reward imbalance (ERI) centres on the balance between perceived effort put in to a particular

job and the rewards that are subsequently received (either financial, in the form of esteem, or as job opportunities or security).

3.3.2 Overall Results

Overall the majority of published evidence favours a link between increased work stress and CAD and strongly suggests a causal relationship. A recent systematic review of aetiologic studies looked at this relationship [30] in 13 prospective cohort studies of over 500 participants per study. Of these three showed no association between work stress and CAD, five studies showed a moderate association (relative risk 1.5 to 2.0) and five studies showed a strong association (relative risk of > 2.0). The adjustments made in these studies were variable, but the majority of these studies were controlled for traditional cardiovascular risk factors, age, smoking, blood pressure and serum cholesterol.

Review of 36 studies published between 1981 and 1993 showed that the majority demonstrated a positive link between job strain and development of CAD for all cause mortality for both blue and white collar workers, men and women[31] although there are still some inconsistencies. More recently, further studies have supported the association [32-34].

3.3.3 Job Strain

Low control has been more consistently linked to increased CAD than its interaction with perceived demands [31 35]. Schnall et al reviewed 25 studies and found associations between job control and CAD in 17 / 25 studies but an association between job demands and CAD in only 8 / 23 studies[31]. Low job control predicts CAD independently of its relationship to SES. Half of the inverse social gradient in CAD incidence is attributable

to low control at work[35], with about one third being attributable to conventional CAD risk factors independent of employment grade itself. Some authors have argued that adjustment for SES weakens or even removes the effect of job-strain [33 36 37]but this view is not universally held[28]. There is an exposure-response relationship between strength of exposure to job strain and the relative risk of future AMI thus adding weight to the theories regarding causality [33 38].

The amount of job control also has influence on life outside the workplace. Workers in jobs with little control over their work have been found to have less participation in socially active leisure and political activities [39]. There is also an association between high job strain and incidence of cigarette smoking [40] and of potentially harmful negative emotions such as depression and hostility [41]

3.3.4. Effort Reward Imbalance

Studies in Finland [33], Germany [42] and the UK [35 43 44] have all now shown significant increases in the risk of CAD with ERI at work. Higher ERI leads to a higher rate of subsequent poor physical and mental health including depression [35] and is predictive of development of CAD [44 36 43 45]. Recently, Kivimaki et al found a 2.2 fold increase in cardiovascular death in those with high versus low job strain and a 2.4 fold difference in risk for those with high versus low ERI[33] after adjustment for age, sex, occupational group, and significant behavioural and biological predictors of cardiovascular mortality.

The exhaustive personal coping style at work due to personal motivation has been termed "over-commitment" [32]. Overcommitment reflects personal attitudes and emotions to work resulting in excessive effort being made often with the hope of approval and increase in esteem. Consequently overcommitment is demonstrated in those who put an

excessive amount of effort into a job for what may be an inappropriately small reward. Overcommitment has been found to have a powerful independent effect on the rates of restenosis following coronary angioplasty, suggesting a link with the body's inflammatory responses [46]

Job strain and ERI have been linked to increased progression of carotid atherosclerosis, (a surrogate of progression of CAD) [47 48] but the evidence is not conclusive. However, Hlatky et al showed no link between job strain and the angiographic severity of CAD[49].

Most of the research done has examined work stress in men. The study of effects in women is more difficult because of the smaller number of coronary events in the working age group. There is a higher incidence of job strain in women than in men [50] and a lower level of control. The majority of studies including the Whitehall II study [28] and a large study of Swedish women [51] show a link between work stress and CAD [50]in women. A recent study of US female nurses failed to show a link between job strain or for job control and CAD incidence [52].

Low social support at home might exacerbate the effect of work stress on CAD [53]. Lack of social support at work has also been associated with an increased risk of CAD [53 54] either as a single factor or in combination with low job control but hasn't been backed up in all studies[28]. Social support was found to modify the effects of job strain in 3 Swedish studies [31].

3.3.5. Marital and Domestic Stress

Stresses at work must also interact with stresses in the home environment. Levels of work stress increase significantly in women proportional to the number of children that

they have at home [55]. Marital stress predicts depressive symptoms in women and there is evidence that women with marital stress have a poorer prognosis with established CAD [56 57]. Marital stress also has a profound effect on social relations in women, with less social integration and support which may have an additive effect on the risk of CAD [58]. The effects of domestic stress are most profound in those women with low SES, poor social support and depression [57]. Women with both domestic and work-related stress have a 5 times greater risk for CAD as women with neither [59]. In an analogous model to the job control model of work stress, it has been shown that women (but not men) with low control at home have an increased incidence of CAD [60] even after adjustment for household social position, smoking, blood pressure, diabetes mellitus, obesity, and exercise.

The large, recent INTERHEART study (a case-control study of over 11 000 cases of first MI) examined four different stress factors; work stress, domestic stress, financial stress, and stressful life events and found exposure related increased odds ratios for the risk of first MI in all cases with population attributable risks of between 8 and 12% independently of variables such as age or cardiovascular risk factors [61]. These stresses were measured by simple questions and revealed a wide global difference in the prevalence of self-reported stress. The study also showed significant effects for depression and for low locus of control (perceived ability to control life circumstances). Other life stresses such as business failure, intra-family conflict, job loss, death of spouse and violence were associated with increased cardiovascular risk.

3.4. SOCIO-ECONOMIC STATUS

Socio-economic status (SES) and the resultant variations in health outcomes is one of the most challenging areas of modern health-care. In an era where we attempt to have a policy of equality for all, any discrepancies in social position and health status raise important questions about the social fabric of our society. SES is a complex concept and is a composite of financial income, wealth, prestige and education. There are many different definitions and methods of assessment of SES which has lead to a lack of conformity of research methods. The strength of association between SES and cardiovascular risk factors is dependent on the definition of social status used [62]. It is important to remember that SES is thought to be responsible for a similar gradient in cancers and other illnesses as well as CAD [63].

3.4.1. Epidemiological Studies

SES is an important and powerful determinant of CAD incidence and outcomes. There is a marked inverse gradient between CAD and SES that has been confirmed in a number of studies [64] [65] [66] [67] with little evidence to the contrary. This association is robust whichever measure of SES is used [62] and may be even stronger in women than men [68].

The premature death rate for CAD is 58% higher for manual workers than for non-manual workers and there are pronounced geographic variations in CAD incidence not only between different countries but within individual countries themselves. The British Heart Foundation estimate that in the U.K. each year 5000 lives are lost in men between 20-64 because of the social disparity in death rates [2]. Obviously this translates into an immense number of extra lives lost each year globally. The recent decrease in CAD

incidence in the Western world has been a phenomenon enjoyed largely by the more affluent classes leading to the greater disparity of a widening of the gap between the social groups[69].

Lower SES is associated with poorer diet, poorer housing, increased obesity, lower levels of physical activity as well as a greater resistance to change risk behaviours [70]. There is greater exposure to crowding and a higher prevalence of crime. Low SES is associated with low social integration and low social activity [65]. High levels of neighbourhood deprivation independently predict the incidence of CAD in both men and women after controlling for age and financial income [71]. A stepwise relationship exists between SES and the prevalence of financial strain, stressful life-events, fatalism and low self-esteem [72]. Consequently, living under these conditions has been theorised as being subject to chronic psychosocial stress and thus many of the resultant mechanisms of disease may be the same.

Traditional cardiovascular risk factors explain only about one third to a half of the risk associated with the social gradient in CAD [62 73]. The discrepancy is almost certainly multi-factorial. Woodward et al found that adjusting for 14 separate and largely traditional risk factors (smoking status, cotinine, alcohol status, type A personality score, leisure activity, diabetes, systolic and diastolic blood pressure, body mass index, total and HDL cholesterol, triglycerides, fibrinogen, and vitamin C consumption) accounted for approximately 75% of the social gradient[67]. A more extensive investigation into the relationship with cardiovascular risk factors was performed with Finnish men. 23 known cardiovascular risk factors (biological, behavioural, psychological and social) were adjusted for [74]. All 23 factors were individually significantly associated with mortality or AMI. This adjustment accounted for the excess in all cause and cardiovascular mortality

but not for the increase in myocardial infarction. The factors adjusted for were biological factors such as body mass index, blood pressure, height, fibrinogen, serum apolipoprotein B, ferritin, copper, blood leucocyte count, haemoglobin, glucose, mercury, triglycerides and HDL cholesterol, health behaviours such as smoking, alcohol and physical activity, psychological factors such as depression and hopelessness, social factors such as social support and marital status, and also factors influenced by childhood such as height. Most of the reduction in relative risk was accounted for by differences in the biological risk factors. Although these data go some way to explaining how the gradient in SES and cardiovascular mortality is mediated, one of the great challenges that lie ahead is to ascertain the reasons why these risk factors are differentially distributed and to ascertain the mechanisms by which they cause disease.

3.5. DEPRESSION, ANXIETY AND CAD

3.5.1. Depression

Depression and CAD are both highly prevalent diseases. Evidence is steadily accumulating from epidemiologic and clinical studies that depression is a prospective risk factor for the development of CAD and that it modifies prognosis after coronary events. Depression is 3 times more common in patients with CAD compared with the general public [75] and it has been estimated that about one fifth of patients with CAD have concomitant depression [76]. About 1 in 3 patients who are admitted to hospital with CAD show some degree of depression and 15-20% of patients suffer major depressive post MI. I will examine here the evidence and mechanisms for the involvement of depression in the development of CAD (discussion regarding the role of depression in patients with established cardiac disease can be found elsewhere [77]).

There have been many studies of depression of varying epidemiologic quality. In the last few years several authors [30] [78-80] have used systematic review as a tool to critically appraise this data. Using a rigorous methodological filter, Hemingway et al identified a possible etiologic role for depression in eight out of eight prospective cohort studies of depression and the development of CAD[78]. Kuper et al found moderate or strong support in 15 out of 22 studies [30] and Wulsin et al found a positive correlation in 9 out of 10 studies [80]. Overall there was a relative risk of approximately two-fold of developing CAD. There is a dose-effect relationship even after adjustment for potential confounding factors [79] [81]. There was a relative risk of 2.69 for AMI or coronary death for clinical depression compared with a relative risk of 1.49 for the presence of depressive symptoms[79]. Despite this dose-effect relationship with events there is little evidence to support the hypothesis that increased depression leads to measurably more severe coronary artery disease. More recently than these well structured reviews, the Honolulu-Asia Aging Study has reported that in a prospective examination of 3196 Japanese American men that there was a 2.3 times relative risk of CAD in otherwise healthy men with depressive symptoms after 3 years and a relative risk of 1.57 at 6 years [81].

There is evidence to suggest that there may be a chronic link with depression pre-dating the appearance of cardiac symptoms, by many years in some cases. The John Hopkins Precursors study followed 1190 medical students for a median time of 37 years and found a median interval of 15 years between the first episode of depression and subsequent first coronary events. The duration of symptoms themselves may also influence the risk of mortality [82].

There has been a great deal of interest in the mechanisms linking CAD and depression and the search to establish causality. Potential psychobiological pathways are discussed in section 3.8. It may indeed be that depression is a causative factor for CAD and this may be done by depression establishing an inflammatory pro-atherosclerotic milieu. However, there are several other ways in which a link might be explained. Alternatives are that the association of inflammatory markers in both depression and CAD may be due to an occult inflammatory process which then initiates CAD and depressive illness, so there may not be a direct causal link. Both depression and CAD could arise from chronic stress in the social environment and this may have an inflammatory mediation. Depression could foster CAD via the adoption of harmful behaviours such as cigarette smoking, poor diet, lack of exercise, and poor adherence to medical treatment. However it is also plausible that these behaviours could promote both the atherosclerotic and the depressive processes. Other less likely explanations include both depression and CAD being the product of widespread atherosclerotic disease or that CAD could be partially a side-effect of treatment with potentially toxic anti-depressant medication. There is also the possibility of reverse causation in that the experience of CAD may itself lead to depressive symptoms.

3.5.2. Related Syndromes

Vital exhaustion (a state of fatigue linked with depressive illness) and hopelessness have been identified as a risk factors for CAD [83]. Vital exhaustion, a syndrome characterized by lack of energy, increased irritability and demoralization [84] has been shown to be predictive of future AMI [85] and is associated with recurrent cardiac events after angioplasty [86]. Tiredness and lack of energy are common premonitory symptoms in the period before ACS [86]. Psychological factors such as hostility and type A behaviour are

associated with an increased incidence of vital exhaustion [86]and exhaustion has been linked to a wider range of inflammatory markers than depression [87] and this may indicate a response to an underlying illness or inflammatory process. Vital exhaustion may be the resultant state after exposure to prolonged or recurrent psychological distress [88] and this syndrome may be a link between stress and heart disease.

3.5.3. Anxiety

Anxiety, like depression is more common in patients with CAD. Data for anxiety and progression of atheroma are conflicting [89 90]. Large-scale prospective studies [91-93 94]have now documented a significant link between anxiety and sudden cardiac death (SCD) with a dose dependant relationship between the level of anxiety and the risk of death. In the Normative Ageing Study [92] men who reported two or more anxiety symptoms had a relative risk of 4.46 (95% CI 0.92 to 21.6) for sudden cardiac death compared with those who did not have the anxiety symptoms. Further analysis of these patients showed significantly decreased heart rate variability in those with higher levels of phobic anxiety [95]. Other studies have however shown no effect of anxiety on CAD development [30]. Anxiety may be analogous to the demand-control model of work stress where there is a chronic perception and worry about not being able to cope. The studies overall have been inconclusive about the possible effects on non-fatal coronary events. The rise of SCD suggests a ventricular arrhythmia as the cause and decreased heart rate variability may play a role in arrhythmogenesis [94 95].

3.6. PERSONALITY, HOSTILITY AND ANGER

3.6.1. Hostility

In the search for a link between personality and CAD, initial interest focussed on type A behaviour, defined by aggression, competitiveness, impatience, time urgency and achievement orientated behaviour [96]. Despite early evidence that type A behaviour may be an independent risk factor for CAD, subsequent literature has been divided with overall evidence being inconclusive to support it as a risk factor [30]. Attention has more recently become focussed upon hostility and anger as the potentially harmful parts of type A behaviour which may influence cardiovascular outcomes.

3.6.2. Epidemiologic Studies

Re-analyses of some of the data from large Type-A studies for hostility have given strong support for hostility as a risk factor for CAD [96 97]. However, the confounding effects of sex, ethnicity, increased fat and calorie intake, decreased physical activity and alcohol and tobacco use make assessing the independent effects of hostility difficult [98] and may weaken initial apparent correlations [99 100], suggesting that a great deal of the excess risk may be from these associated health behaviours which are more common in hostile groups. Social support is another powerful moderator of the effect of hostility on cardiovascular outcomes [101].

Some studies show a positive correlation between hostility (assessed in several different ways) and CAD. However, critical examination of the prospective studies found no robust overall evidence for type A behaviour or hostility as a factor in the development

or prognosis of CAD[30 72 75 102-104] after adjustment for confounding factors. Some evidence suggests that hostility may play a part in CAD diagnosed in younger patients [102]. Ketterer et al [105] found that high hostility scores were associated with a premature diagnosis of CAD. The effect of hostility decreases as people get older [106]. Recent prospective comparison of French and Northern Irish populations have shown no evidence to support hostility as a causal factor in CAD [107].

Examinations of coronary calcification has also shown results both supporting and refuting a link with hostility [108 109]. Hostility has also been reported to affect carotid artery intimal thickness [110] and to predict restenosis after PTCA[111] but again results have been mixed and subject to confounding factors and social support[101].

3.6.3. Anger

Just as examining hostility has been a refinement of looking at the type A personality construct, investigators have examined the expression and experience of anger (a related concept to hostility) to try and define the harmful personality and behavioural components. Whereas hostility is a characteristic of a person and is manifested in aggressive behaviour, anger has both trait and state facets. Anger is quite a complex entity having not only trait elements (such as "angry temperament") but also differing frequency and strength of expression as well as methods of expression (such as "anger-in" and "anger-out"

Although studies have examined different facets of anger to attempt to isolate the harmful components there is as yet no general consensus on whether it is anger-in, anger out, anger proneness, anger-temperament anger-reaction or any of the other "anger constructs" which are the most important

3.6.4. Epidemiologic Studies

The current literature on anger is much smaller than that for type A behaviour or hostility but shows a more consistent association with CAD. Anger is associated with a 2 to 3 fold increase in the risk of development of angina, AMI or SCD, with a dose response relationship between level of anger and risk[112]. Data collected from medical students as part of the John Hopkins Precursors Study showed that anger is prospectively and independently associated with premature cardiovascular disease in young men with a relative risk of about 3 fold compared with non-angry men [113].

Normotensive people with high trait anger (a relatively stable personality trait) are 2.2 times more likely than those with low anger to develop CAD [114] with a dose-response relationship again being seen. An association was not seen in hypertensive individuals although this may have been due in part to protective effects from anti-hypertensive medication. The effect of beta-blockers has been contradictory thus far [112 115]. It may be that the effect of anger is to some extent mediated by the same pathophysiological factors as hypertension.

Analysis of data from the Atherosclerosis Risk in Communities Study (ARIC) looked at the two components of anger proneness as assessed by the Spielberger Trait Anger Scale: anger-temperament and anger-reaction. Angry temperament (tendency towards quick, minimally provoked or provoked anger) was associated with an increased relative risk of 2.3 for MI or fatal CAD in normotensive subjects after adjustment for traditional CAD risk factors [116]. This gave a risk similar to that of hypertensive patients regardless of their anger levels. Persons with an angry-temperament experience anger for longer and more

intensely than those prone to angry reactions. Consequently the pathophysiological effects of angry temperament may be more sustained. An angry temperament however is relatively infrequent with only 6% of the ARIC population reporting it.

It may also be the way in which individuals cope with and express their feelings of anger that is important. There are 2 basic styles of coping with anger:- "anger in" where the individual internalizes their angry feelings and does not express them to others, and "anger out" which is typified by the expression of anger. Overall the evidence examining anger-in and anger-out against outcomes such as CAD and onset of hypertension has been inconsistent. Similarly the evidence for anger traits and CAD do not give us a consistent answer. Anger-in and potential for hostility have been significantly associated with angiographic extent of CAD disease severity [117]. Both anger-out and suppressed anger are predictive of incident CAD [118 119]. There has been recent interest as to whether both of these extremes of expression may both actually be harmful to health. A recent study of 23,522 health professionals found that men with moderate levels of anger expression had a reduced incidence of non-fatal MI than those with lower levels of expression [120]. Extremes of either anger-in or anger-out have also been associated with progressive increases in future hypertension [121].

3.7. SOCIAL SUPPORT

Social interactions govern our everyday lives whether it be with friends or family, group or organisational activities. Social contact is vital for shared interests and friendship, as well as practical and emotional support. The concept of social support as regards health outcomes is complex and relates to emotional and material support, care giving and receiving, and also health behaviours. Both emotional support from very close persons

("attachment") as well as support provided by an extended network of acquaintances ("social integration") may be important [122].

In England 16% of men and 11% of women report a severe lack of social support. Persons in unskilled manual jobs are more likely to have low social support than those in professional employment. Adults from South Asian or Chinese communities in the U.K. are twice as likely as Whites to have low social support [2 123].

As well as the positive sides of social interaction, one must bear in mind that persons with less social contact may have had bereavements or psychologically upsetting events which may have separated them from friends and loved ones leading to a diminution of social contact. These negative events may lead to consequent psychosocial stress which contributes to the cardiovascular risk. People who are ill may withdraw from society and thus there is a chance that isolation may follow illness rather than the other way round.

3.7.1. Epidemiological Studies

Many types of social support have been examined using different methodologies, but despite this the results in men have been remarkably consistent and the evidence in women is similarly growing. Systematic review has supported the concept that poor social support increases the risk of CAD. 6 out 7 prospective aetiological studies reporting hard end-points for CAD analysed by Kuper et al showed independently increased risk in persons with social isolation [30]. Rozanski et al analysed a wider 15 studies finding a positive and independent association in almost all cases [75]. There is also a large amount of retrospective work linking social networks to CAD but this is obviously more prone to sources of bias. For example, analysis of survivors post myocardial infarction in the Beta Blocker Heart Attack Trial [124]showed a fourfold rise in

cardiac mortality in those who were socially isolated and had high levels of stress. This stress and isolation was most prevalent among more poorly educated men.

The overall relative risk of developing CAD due to lack of social support is of the magnitude of approximately two to three-fold. Social support remains a robust and statistically significant predictor of coronary events after controlling for conventional cardiac risk factors as well as exercise, weight, and social and behavioural demographic risk factors. Causation is supported by evidence suggesting an inverse gradient in the amount of social support and the subsequent incidence of CAD [75].

Evidence to suggest that social isolation is associated with increased angiographic disease severity is not consistent [125 126]. In women post AMI social isolation is positively associated with more numerous and more severe coronary artery stenoses [127].

Meta-analysis has suggested that quality is possibly more important than quantity of social support [128]. The degree of emotional support that one receives from one's social network is also important and may be additive to the size and frequency of interactions [129]. It is also possible to gain some important support from non-human sources, and there is a likely benefit from pet ownership [130].

Evidence for an additional interactive effect of negative life events comes from a prospective study of 752 men over 7 years that showed an increase in all cause mortality for those who had had a major life event in the year before baseline examination. This association was only present for men with low emotional support however [131] and suggests that high levels of emotional support are protective from the consequences of stressful events.

There is likely to be interaction between the social support and other psychosocial risk factors, as they tend to cluster together. Social isolation and depressive symptoms have been shown to interact, predicting recurrent cardiac events in women with CAD independently of age, severity of symptoms and traditional cardiovascular risk factors.,[132 133]. Social support moderates the effects of job strain and depression on CAD incidence and lack of social support at work is also associated with an increased risk of CAD [53 54 134]. There is increased psychological distress in persons who report a lack of social support [135]. Progression of established CAD is more severe when low social support is combined with outward anger expression [136].

Socially isolated people are more likely to have lower income, higher hostility ratings and have a greater incidence of harmful behaviours such as cigarette smoking and poor diet. Persons with low social integration were also more likely to be diabetic, be less physically active and more surprisingly, have lower body mass index and serum cholesterol [122]. Patients who live alone have significantly longer times from symptom onset to arrival at hospital and fibrinolytic treatment [137]. There may be poorer compliance with medication and medical advice in those who live alone. Persons who live alone may be less likely to seek medical advice in the event of illness. People with a greater network of friends and acquaintances tend to have healthier lifestyles and may have greater coercion and support to seek and comply with medical advice and treatment [137a,b]. They may also have a greater motivation to keep themselves well if they have family and dependents who rely upon them for care or financial security. Thus it is difficult to investigate the impact of one psychosocial factor independently of others.

3.8 MECHANISMS

Full consideration of the role of psychosocial factors in CAD not only involves scrutiny of the epidemiological research, but also an understanding of the mechanisms through which social and psychological factors impact on coronary atherogenesis and the initiation of acute cardiac events. Several biological pathways relevant to the development of CAD are sensitive to psychological stress, and this provides a starting point for delineating the mediating mechanisms.

3.8.1 Hypothalamic-Pituitary-Adrenal and Sympathoadrenal Axes

Cortisol secretion is one of the primary metabolic responses to psychological stress. There is cortisol hypersecretion in depression, work stress, hostility and in men of lower SES [75 138 139]. Although cortisol usually has an anti-inflammatory action it may be that with chronic over-secretion that resistance develops, together with impairment of feedback control. Hypothalamic-pituitary-adrenocortical (HPA) axis function is disturbed in obesity and insulin resistance, and it has been postulated that this dysfunction is driven by heightened stress activation [140].

It seems likely that a large part of the harmful effect of stress is mediated by the sympathetic nervous system and circulating catecholamines. Work stress, chronic anger and hostility are related to increases in plasma epinephrine and chronic sympathetic activation [75 141]. The sympathetic activation and increased catecholamines found in many cases of depression may activate platelets, activate macrophages upregulate expression of inflammatory molecules such as IL-6 [142] and also contribute to abnormal

vascular endothelial function, the development of hypertension [116], and glucose intolerance.

3.8.2 Hypertension and Blood Pressure Reactivity to Stress

Given the link between chronic stress and the HPA and neuroendocrine systems, hypertension is a potential mediator of the effects of psychosocial stress on CAD. Hypertension varies with SES in almost all studies [143] and work stress is a risk factor for hypertension [144 145]. Anger expression and depressive symptoms are also associated with hypertension [121 146].

Ambulatory blood pressure and pulse rate differ with SES. Lower SES men in the Whitehall II study were shown to have a greater ambulatory BP and pulse rate in the morning independently of physical activity [138], despite no difference in resting blood pressure. Job strain affects ambulatory blood pressure in a dose-response relationship, with the effect persisting beyond working hours [144].

There has been much recent interest in the concept of cardiovascular reactivity to and recovery from stress as important factors through which vascular damage can occur. The magnitude of cardiovascular stress reactions does not seem to vary with SES, but there is delayed post-stress recovery in lower SES groups, mediated by increased total peripheral resistance [147]. These responses may be due to already impaired vascular endothelial function and may be an early sign of future clinical disease. Women with elevated depression scores exhibit heightened reactivity and recovery, associated with greater catecholamine stress responses [148]. It is conceivable that heightened cardiovascular reactivity and delayed recovery translate into an enhanced triggering mechanism for

acute coronary events. Sustained or transient hypertension could be injurious to endothelial function, promoting atherogenesis. Greater cardiovascular stress reactivity has been associated with job stress [149] and anger [150] as well, and men with larger stress reactions and high job demands show more rapid progression of carotid atherosclerosis [151].

3.8.3 Endothelial and Vascular Function

Endothelial-dependent flow mediated dilatation of the brachial artery is a marker of vascular endothelial function, and is impaired in depression. This effect does not alter with anti-depressant treatment despite restoration of mood [152], [153] suggesting that the mood alteration may not be the primary disturbance of depression but a manifestation of a more fundamental underlying problem. An acute episode of mental stress can cause reversible impairment of endothelial function for up to 1.5 hours in healthy individuals [154]. Depression is associated with higher levels of intercellular adhesion molecule-1 (ICAM-1), E-selectin and monocyte chemoattractant protein-1 (MCP-1) [153]. It also increases monocyte expression of pro-inflammatory cytokines and chemokines [155] which may have a role in the cellular infiltration of the endothelium. It may be that depression (like low SES, work stress and lack of social support) acts as a chronic stressor leading to prolonged endothelial dysfunction and consequent abnormalities of cellular adhesion, migration and proliferation, resulting in a persistent pro-atherosclerotic environment. Beta-1 adrenoceptor activation may mediate some of the detrimental endothelial effects of psychosocial stress [156].

3.8.4 Inflammation and Immunity

There is a great deal of evidence that CAD is an inflammatory disease [9] [157]. C-reactive protein (CRP) and plasma interleukin 6 (IL-6) prospectively predict coronary events in asymptomatic populations [158-160]. CRP is elevated in lower SES persons compared with their higher SES counterparts [161]. Recent analysis of a sub-group of the Whitehall II study has shown that plasma IL-6 and CRP are inversely related to social position [162]. CRP, IL-6, tumor necrosis factor-α (TNF-α) and interleukin-1 receptor antagonist (IL-1Ra) are all raised in depressed patients [163] [164]. This effect is independent of smoking, infection, and established cardiovascular risk factors. The pro-inflammatory cytokines may be responsible for some of the somatic features of depression as they can cause anorexia, malaise, weight loss and sleep disturbances as well as mood alterations. Depression also interacts with obesity to cause elevated CRP levels [165]. Several forms of chronic or episodic life stress are accompanied by increases in IL-6. For example students sitting academic examinations [166], people looking after dementing relatives [167] and people with post-traumatic stress disorder [168] have all been demonstrated as having raised IL-6 levels. Hostility and aggression, but not anger are associated with an increased TNF-α expression to lipopolysaccharide stimulation [169], adding weight to the theory that there may be a biological as well as a haemodynamic hyperreactivity contributing to CAD in some individuals.

3.8.5 Platelets and Coagulation Factors

Platelet activation is increased in depression, with higher levels of platelet factor 4 and beta-thromboglobulin [170], increased activation of platelet glycoprotein IIb/IIIa receptors and increased 5HT-mediated platelet activity [171]. Men of lower SES have greater platelet

activation under resting conditions as assessed by platelet-leukocyte aggregates, although the magnitude of response to mental stress does not change with SES [172]. The stress of increased workload is also associated with increased platelet count and aggregability [173]. Anger has been linked to increased platelet aggregation under conditions of mental stress [174], while aspirin lowers the risk of CAD associated with anger [112 115].

Von Willebrand factor has an inverse relationship with SES, an effect only partly explained by biological factors or other health related behaviours [175 176]. Increased workload causes a hypercoagulable state with increases in factor VII and factor VIII [173]. Work stress can also lead to impaired fibrinolysis (decreased tissue plasminogen activator and increased plasminogen activator inhibitor antigen levels) [177]. There are differences in this psychobiological reactivity associated with socioeconomic position. Mental stress elicits more prolonged increases in prothrombotic variables (Factor VIII, plasma viscosity and whole blood viscosity) in lower SES groups [178], suggesting that this could be a mechanism through which lower socioeconomic position results in higher CAD risk.

3.8.6 Fibrinogen

Several large studies have found a positive association between fibrinogen and work stress [179-181], although others [177 182] have failed to show any relationship. A recent large Belgian study suggested at least part of the effect of job strain (and potentially other psychosocial stressors) on fibrinogen is mediated by its effect on other risk factors [183]. Workers with low job control have an exaggerated fibrinogen response to mental stress compared with workers with higher job control [184]. Depression and social isolation are

associated with higher levels of fibrinogen, an association which remained robust after adjustment for potential confounding factors [87] [122].

3.8.7 Lifestyle Factors

Smoking shows a very strong social gradient [185]. Increased job strain, low SES, social isolation and depression have been linked with unhealthy behaviours such as smoking, physical inactivity and high fat intake [40]. Depression and social isolation are associated with diminished physical activity [186], while effort-reward imbalance correlates with increased body mass index [33]. Diet varies greatly with SES, with less consumption of fruit and vegetables in lower SES groups [2]. Several of the risk factors for CAD in adults are elevated in children of lower SES, including cigarette smoking, lower birth weight, greater adiposity, and poorer diet [187]. Socially isolated people are more likely to have lower income, higher hostility ratings and have a greater incidence of cigarette smoking and poor diet than others. Patients who live alone have significantly longer times from symptom onset to arrival at hospital and fibrinolytic treatment [137], poorer compliance with medication and medical advice.

3.8.8 Lipids

Anger, mental stress and low SES have been linked to atherogenic lipid profiles [188] [189] [190]. Most studies on work stress have found little or no effect on lipids or on glucose intolerance [191]. The WOLF study was devised to specifically examine work stress and lipids and found an adverse relationship in the ratio of LDL to HDL cholesterol in younger men and women only [182]. More recent work has suggested that respite from work stress favourably alters lipid profiles in chronically stressed individuals [192].

3.8.9 Diabetes and the Metabolic Syndrome

The metabolic syndrome shows an inverse social gradient [176]. In the Whitehall II epidemiological study, the odds ratio for having the metabolic syndrome was 2.2 for men and 2.8 for women when comparing the lowest with the highest employment grade. Depression and anger prospectively predict development of the metabolic syndrome in women [193] and diabetes is more common in depressed than nondepressed CAD patients [76]. Acute mental stress impairs insulin sensitivity and repeated sub-acute episodes could lead to a similar metabolic effect as impaired glucose tolerance and the metabolic syndrome [194]. Additionally, diabetic patients with depression are 3 times more likely than their non-depressed diabetic counterparts to develop CAD [195] due to differences in insulin resistance, autonomic dysregulation, inflammation and smoking [196]. Persons with low social integration are also more likely to be diabetic [122]. Theoretical work has suggested that in some cases the metabolic syndrome nay mediate the link between chronic stress and CAD [197]. Recent work [198] has identified an important link between hyperglycemia and raised levels of inflammatory cytokines which may explain some of the excess risk of vascular diseases suffered by patients with diabetes and impaired glucose tolerance.

Increased sympathetic activation is a likely culprit for much of the pathophysiological effect of psychosocial factors. Sympathetic activation may mediate the link between psychosocial stresses and CAD. Sympathetic activation leads to increased insulin resistance [198a-c]. Brunner et al have assessed the link between psychosocial factors and the metabolic syndrome[198d]. They found that increased sympathetic autonomic activity was a potential mediating mechanism. They calculated that psychosocial factors

accounted for 37% of the link between the metabolic syndrome and increased sympathetic activity and surmised that this was a powerful potential pathway to translate the effects of psychosocial stresses into increased CAD. This same study also showed a relationship between the sympathetic outflow and IL-6 levels reinforcing the concept that there are likely to be multiple causal mechanisms in the link between psychosocial factors and CAD.

This link between diabetes and autonomic control may also be important in ACS. Diabetic ACS patients have recently been shown to have higher heart rate and blood pressure than non-diabetics which may also translate into increased ischaemia and poorer prognosis in this group[198e]. The total interaction between autonomic activity and diabetes / the metabolic syndrome is ultimately likely to be a complex one with sympathetic discharge influencing insulin resistance but then diabetes itself affecting the autonomic nervous system by neuropathic processes.

3.8.10 Other Possibilities

Recent work has shown a link between polymorphisms of the angiotensin I converting enzyme and the G protein beta3-subunit genes. Both of these have variants associated with both depressive and cardiovascular disorders. The combination of ACE ID / Gbeta3 TT genotypes increased the risk of depression significantly and may be a link with vascular disease [199]. Lewthwaite et al showed an increase in heat shock protein 60 a possible marker of susceptibility to CAD in civil servants with social isolation or lower social status [200]. Hyperhomocysteinemia as well as decreased folate and vitamin B12 have been related to depressive symptoms [201]. Plasma homocysteine levels are positively associated with both hostility and anger [202].

The discovery of functional polymorphisms for genes regulating beta-adrenoceptors, platelets and cytokines make a genetic component to the risk of CAD development with psychosocial stress increasingly likely. There is still much work to do in elucidating the role of these factors. The recent finding that stressful experiences lead to depression dependent on functional polymorphisms of the serotonin transporter gene [203] is especially exciting.

3.9 INTERVENTION STUDIES

Having identified that psychosocial factors exert a negative effect on the incidence of CAD and its prognosis, the next important step is to see whether these factors can be manipulated by drug therapy or by behavioural or social manipulation. The success of any interventions into these psychosocial factors associated with CAD has been disappointing so far. For most psychosocial problems any social manipulation or intervention is a difficult, costly and time-consuming process.

Depression may be more amenable to change than some other psychosocial risk factors, since pharmacotherapy is efficacious and that depression has demonstrated underlying biochemical abnormalities. Unfortunately several of the more traditional drug treatments, such as tricyclic antidepressant drugs for depression have significant cardiovascular side-effects and so cannot be used in CAD patients[204]. Extra medication is always a concern in cardiac patients as they will often be taking several cardio-active drugs such as platelet inhibitors, statins, beta-blockers and ACE-inhibitors and so the potential for adverse drug interactions is increased and must always be considered. One group of drugs however, the selective serotonin reuptake inhibitors (SSRIs) have been shown to be safe and have been assessed in several trials. The data from trials of SSRIs in patients with

cardiovascular disease has recently been the subject of systematic review [205]. SSRIs seem to be safe and effective for the purpose of treating depression in cardiac patients however there is still a definite lack of evidence that treating depression in patients with CAD improves outcomes. Two studies have shown a non-significant trend in the reduction of cardiovascular events with SSRI treatment of depression in a post-MI population [206 207]. The reason for this is partly that none of the trials have been sufficiently powered with large enough patient numbers or large enough number of coronary events in the study groups.

The SADHART (Sertraline AntiDepressant Heart Attack Randomised Trial) study [207] was initially devised as a safety study and was not designed to be large enough to show a benefit on adverse cardiac events. SADHART [207] showed that although SSRIs successfully alleviated depressive symptoms, this did not translate into a significant change in the incidence of cardiac events in post-MI patients, although there was a non-significant decrease in serious cardiac events in the sertraline group. Treatment with of depression after AMI with SSRIs does however produce a significant improvement in quality of life measures [208] and has been shown to decrease hostility scores [206]. SSRIs have also shown a benefit of having inhibitory effects on platelets [209] and of increasing heart rate variability in patients with CAD which could have a benefit on the incidence of dysrhythmic death [210]. Depressed persons display an exaggerated serotonin-mediated platelet reactivity [171] and the effect of sertraline induced serotonin receptor inhibition could partly explain the trend towards benefit seen in the SADHART study [207]. In a sub-group of the SADHART study, markers of platelet and endothelial function were assessed in patients treated with sertraline and controls. Significantly less β-thromboglobulin and P-selectin were seen in the treated group suggesting a reduction in

platelet and endothelial activation [211]. There was widespread use of both aspirin and clopidogrel in both groups suggesting an additional benefit of sertraline.

It is interesting that Broadley et al [152] observed impaired endothelial function in depressed patients, even though depression had been effectively treated. Other groups have also found that treating depression does not reverse all of the accompanying pathophysiological abnormalities. Maes et al [212] found that anti-depressant treatment did not significantly reduce the raised serum IL-6 or IL-1 Ra levels in depressed patients, although the elevation in IL-6 was more pronounced in the patients with treatment resistant depression. Similarly, effective treatment is not associated with normalisation of the abnormalities of heart rate variability [213] or baroreflex sensitivity [152] seen in depression. It is probable that treatment for depression will not reduce mortality and morbidity from CAD unless it tackles the underlying link between depression and CAD, rather than just the symptoms of depression. Medication affecting the symptoms alone may have limited benefits which need to be balanced against deleterious effects. It may be that some depression in cardiac patients is a manifestation of an underlying inflammatory process, and that treating the symptoms does not necessarily treat the crucial elements of the disease. These preliminary treatment findings indicate that much more research needs to be done before specific interventions to reduce psychosocial risks for CAD can be recommended. However further studies are currently underway, including a large trial to follow on from the SADHART study which will hopefully yield more definitive evidence.

As well as pharmacological therapy, cognitive behavioural therapy (CBT) has also been used to attempt to reduce the incidence of adverse cardiovascular outcomes. Behavioural therapy has many potential advantages and can be used to target risk factors, health

beliefs and positive lifestyle changes as well as to attempt to positively influence psychosocial functioning and quality of life. This work has largely been done in a post MI population. Initially several small trials showed beneficial results with decreases in cardiac death and repeat MI from either group psychological therapy or from telephone based intervention [214-216]. Johnston et al showed that nurse led counseling could produce measurable decreases in depression, anxiety and disability post MI [217]. Interest in the area was further stimulated by the aggressive lifestyle and behavioural modifications proposed by Ornish in several studies which showed beneficial effects on cardiovascular risk factors, cardiovascular events, degree of coronary artery stenosis and decreased need for revascularization therapies [218-221]. However it is difficult to ascertain the exact contribution that stress management and CBT had in the context of widespread lifestyle alterations involving actions on factors such as exercise and diet as well.

Two meta-analyses of psychosocial interventions post MI revealed a decrease in mortality and morbidity. Desseldorp et al [222] analysed 37 studies of psychological therapy for patients with ischaemic heart disease and found a decrease in cardiovascular events although they did not find a benefit in patient with depression or anxiety. Linden et al [223]examined the effects of psychosocial interventions on top of exercise rehabilitation and found an improvement in cardiovascular risk factors such as blood pressure, pulse rate, and cholesterol as well as improvement in psychosocial functioning and decreased cardiac death.

Larger individual trials have been performed to examine the role of CBT with differing results. The Recurrent Coronary Prevention Project randomized 862 post AMI patients to specific psychological counseling or conventional cardiac counseling and found that those in the psychological counseling group had a benefit in psychological well-being as

well as a 44% decrease in the incidence of death and non-fatal MI [224]. The M-HART (Montreal Heart Attack Readjustment Trial) however enrolled 1376 post MI patients to intensive home health nursing intervention compared with conventional treatment. Although there was a small improvement in the symptoms of depression there was no alteration in cardiovascular outcomes for men, and women actually had a higher rate of cardiac and all cause mortality in the intervention group[225].

The ENRICHD (Enhancing Recovery in Coronary Heart Disease Patients) was specifically designed to see if early intervention with CBT supplement with SSRI use as appropriate could reduced cardiovascular mortality and recurrent MI in post MI patients with depression and / or low perceived social support (LPSS)[226]. 2481 patients with depression and or LPSS were randomized to either conventional care or to CBT and / or sertraline treatment for depression as appropriate. 39% of their total population was depressed post MI with 26% reporting LPSS and 34% both. Anti-depressants were prescribed to 20% of the conventional care group and 28% of the intervention group by the end of follow-up. There were overall improvements in psychological and social functioning (as evidenced by improved LPSS and depression scores), but no significant difference in cardiovascular endpoints. There was a trend towards reduction in cardiovascular death with a hazard ratio of 0.83 (0.64 – 1.1).

One of the interesting findings was that whilst there was a trend in men and in whites to benefit from CBT, the trends favoured usual care in women and patients from ethnic minorities. Recently a subgroup analysis from the ENRICHD study has been published showing a significant effect of treatment efficacy for white men for the combined endpoint of cardiac death or non-fatal MI [227]. In contrast there was no significant effect for white women or for ethnic minority patients of either sex. These differences

remained after adjustment for factors such as depression, hypertension, social isolation, co-morbidity, education and ejection fraction. It may be that interventions will have to be tailored to be sex and culturally specific if they are to be efficacious. Pharmacological anti-depressant therapy was however associated with a lower risk if re-infarction and / or mortality (adjusted hazard ratio 0.63 95% CI 0.46 to 0.87) which correlates with the SADHART [207] study and other data [228]. However it is important to note that the use of antidepressants in this trial was not randomized. It is possible that the high use of anti-depressant drug use in this study masked any benefit that CBT may have had. It may also be that treatment duration of longer than the 6 month period of this trial is needed.

Similarly a randomized trial of psychological rehabilitation post AMI in 2328 patients showed no difference in clinical sequelae at one year although interestingly, the clinical prevalence of anxiety and depression remained high at follow up whereas most other studies have shown a beneficial effect in the reduction of adverse psychological parameters[229]. A recent trial of exercise and stress management in patients with proven CAD and evidence of ambulatory or mental stress-induced myocardial ischaemia has shown a reduction in CAD events [230], although it is hard to extricate the separate components of mental and physical interventions.

Interventions into reducing job strain may be difficult and researching the effects of intervention more difficult still. There is some evidence that stress management training at the workplace can help reduce blood pressure[231] and in atherogenic lipids[232], however there is little evidence as yet to support intervention into work stress as having an effect on any hard end points.

Psychological interventions for coronary heart disease has been the subject of a recent Cochrane review [233]. The review found that there were 36 randomised controlled trials

with a total of 12,841 patients. Half of the trials were stress management studies and overall the reviewers felt that many of the trials were methodologically poor. Overall psychological interventions showed no evidence of effect on total or cardiac mortality but did show small reductions in anxiety and depression in CAD patients. There may also be benefits to quality of life but the number of studies reporting data on this has been small.

Consequently the challenge remains to try and identify patients who may benefit from psychosocial and / or pharmacological interventions. It may be that a well powered study into use of SSRIs in depression post MI may provide conclusive evidence of benefit. Further work is needed with CBT to try and identify which patients may benefit from specific interventions in addition to the current lifestyle and educational counseling given as part of patient rehabilitation post MI.

3.10. LIMITATIONS OF THE CURRENT LITERATURE

Although there are huge amounts of published data, they are of vastly differing methodological quality. The number of adequately sized prospective studies is relatively small. It is for these reasons that particular attention has been paid to the systematic literature reviews. Because of the nature of the exposures being examined, most of the studies are retrospective with often no good control group. The possibilities of publication and selection biases are as always present. Finally the intricate relationship between many of the features mentioned above and the presence of multiple social, environmental and behavioural confounding factors make analysis of the results difficult even when attempting to statistically control for potential interactions.

Studies of association, often retrospective are inevitably highly confounded by the interaction between psychosocial factors and disease severity, symptoms and functional status, co-morbidities, treatment and compliance [234]. Further confounding comes from interaction between the psychosocial factors themselves. Corrections for these factors are relatively crude. Methodologies are numerous and poorly standardized with questionable validity between different populations, sexes and cultures. An interesting study into the potential inherent bias in studies of psychological factors was performed recently by Macleod et al [235]. They argued a role for reporting bias finding that in a prospective observational study, participants with higher self-reported levels of stress were more likely to report symptoms of CAD and to bias results in the absence of hard evidence. This however only applies to subjective end-points such as symptomatic angina and does not apply to the reporting of hard end-points such as AMI and death. Other authors have however found that perceived mental stress is predictive of cardiovascular and cerebrovascular events [236] [237].

One of the problems in assessing the epidemiological data is that even in the best designed prospective studies there is a period of life before entry to the trial, so that birth and early life factors may have already had an influence. This early life period is important to the psychological and social make-up of an individual, and many health behaviours and attitudes are formulated in early life. Early life adversity also has an impact on adult biological stress reactivity and on cardiovascular risk profiles [238].

Some epidemiologists have challenged the "psychosocial hypothesis" that these factors influence physical health outcomes [239]. There are arguments regarding bias and confounding making the observational evidence difficult to interpret and pointing out that intervention trials have largely been unsuccessful. It can be hard in many of the

studies in this area to control for subjectivity in participant responses and for "complaint tendency", and also that causality is very difficult to prove. Systematic review has shown that interventions to attempt and reduce work stress, mostly by increasing job control, have so far largely been ineffective [240].

3.11. SUMMARY

There are now convincing data to support a link between SES, social support, depression and work stress and CAD. There is growing evidence to support a link with anger. The wide variation in results relating to hostility prevents any concrete conclusions being made at this time. It is often difficult to isolate the effects of independent psychosocial variables as they interact and tend to cluster together with features such as low socio-economic status, depression, work stress etc co-existing. The more negative the psychosocial profile, i.e. the more of these detrimental psychosocial variables possessed, the greater the risk of CAD. In the Kuopio study persons with one or two psychosocial risk factors were twice as likely to die as those with none during the follow up period, but those with three psychosocial risk factors were four times as likely to die [241]. Social isolation and depressive symptoms interact to predict recurrent cardiac events in women with CAD [133]. Social support moderates the effects of job strain, anger and depression on CAD incidence, and lack of social support at work is particularly associated with raised CAD risk [53 54].

It is very likely that the effect of psychosocial factors on atherosclerosis is further modified by individual differences in genetic phenotype with different functional polymorphisms working to moderate or exaggerate the effects of external influences on

the physiological mechanisms and pathways important to the disease process, thus further explaining the inter-individual variation in prevalence of CAD.

The evidence discussed in this chapter has helped to drive the research studies detailed later in this thesis in several ways. Traditional lifestyle factors and cardiac risk factors do not fully explain the incidence of coronary artery disease and so it is of importance to delineate how factors in the social environment can affect acute disease processes. We have seen how psychosocial factors are implicated in the progression of chronic atherosclerotic disease but what is interesting to the acute physician is how these factors dictate the manifestation of ACS, not only in its timing, but also with regard to the underlying psychobiological mechanisms and pathways that mediate these effects.

Chapter Four

THE EVIDENCE FOR TRIGGERING OF ACUTE CORONARY SYNDROMES – TEMPORAL VARIATION

4.1 INTRODUCTION

In order to learn more about the factors implicit in the triggering of acute coronary syndromes (ACS), it is important to examine not only the effect of external psychological, physical, behavioural and environmental factors, but also to look at the endogenous variation in onset. Examining these patterns may make it easier to understand the factors involved in the onset of ACS, including the underlying physiological and biochemical mechanisms, and thus may give ideas for ACS prevention. It is likely that these patterns are a product of endogenous physiological changes which predispose to ACS onset which may be then modified by external triggers. Consequently, this chapter examines the temporal distribution of ACS looking at the seasonal, weekly and circadian patterns and links these patterns to underlying pathophysiological mechanisms which may be involved.

4.2 CIRCADIAN VARIATION

4.2.1 Circadian Variation in ACS

Initial information about circadian variation came from analysis of thrombolytic trials; the MILIS [7] and the ISAM [242] studies which showed an increased incidence of AMI in the morning. This has been supported by many other studies, and almost 25% of all acute myocardial infarctions (AMI) occur within the first 3 hours of waking [243-248]. A meta-

analysis of AMI timing has suggested that nearly 9% of all AMIs are attributable to this morning excess [249] with a relative risk of 1.4 compared with all other times of the day [242], and a relative risk of between 2 and 3 compared with late evening. The morning peak is present irrespective of age, sex or severity of CAD, although there are some group variations in incidence which are discussed later in this chapter. Most studies have assessed the morning as the time between 6.00am and 12.00pm. However, specifically adjusting analysis for time of waking, a period of vulnerability is identified with an approximately 3-fold increased risk of myocardial infarction in the first 3 hours after waking[245]. There is also a reduced myocardial threshold to ischaemia, and more episodes of ischaemia on ambulatory monitoring in the morning than at any other time [250]. Ventricular dysrhythmias and sudden cardiac death are also more likely to occur in the morning than at any other time of day [251 252]

Other studies have suggested the existence of two separate morning peaks; the first early morning at around 07.00 and the second late morning at around 10.00. This may reflect a difference in waking times, although was not different in working versus retired persons [243]. The MONICA project data showed that the morning peak may be later on a Sunday than on other days of the week [253], reinforcing the likely link with waking time.

One of the initial concerns about the data was that there was an apparent increase in morning infarction because of delayed presentation, inaccurate patient reports of onset time or infarct onset when the patient was sleeping. Because of these issues regarding reporting bias, studies have assessed both patient reporting of the onset of chest pain as well as the use of creatine kinase (CKMB) curves to mark the time of onset of infarction [242 254 7]. Studies show a good correlation between the two, but a more pronounced pattern of diurnal variation using the CKMB curves [7]. Daytime infarcts are more likely to have

possible external triggers than those occurring in the evening or night-time, although there is no difference in the reported incidence of potential triggers between morning and afternoon infarcts [254].

4.2.2 Alterations in the Pattern of Circadian Variation

The morning excess of AMI is absent or diminished in some groups such as diabetics and smokers [244 248 255] but this has not been a universal finding [7]. Rana et al found that the morning peak was diminished in type 1 diabetics and type 2 diabetics of over 5 years standing but not recently diagnosed type 2 diabetics [256]. The morning peak is also attenuated by prior aspirin and beta-blocker therapy, reinforcing potential links with the autonomic nervous system and with platelet activity.

A second evening peak, between 6pm and midnight, in addition to the morning peak has been seen in several [243 254 257-259] but not all studies [242 244 245 255]. In some of the same subgroups (smokers, diabetics and those taking beta-blockers) who display a blunted morning peak [244 248 260], this evening peak is of approximately equal magnitude to the morning peak in the incidence of AMI. There is controversy and conflicting data regarding the pattern in the elderly, women, and those with previous MI or heart failure [7 242 248]. The evening time was the peak time of infarction for patients sustaining a non-Q-wave myocardial infarction (NQWMI). The second peak occurs at 9 and 15 hours after waking [243 257] and is probably also related to waking time. It may be that different pathophysiological and psychosocial mechanisms underlie events in the morning and evening.

Several physiological functions undergo a natural circadian rhythm that may lead them to act as acute risk factors and predispose to morning infarction and these are discussed later in this chapter.

4.2.3 The effect of Aspirin

Aspirin therapy reduces the morning incidence of AMI [255] [257]. The Physicians' Health Study [257] showed that prior aspirin therapy caused an overall reduction in the incidence of AMI over the course of the day, and reduced the morning incidence of MI by 59% compared with 34% at other times [257]. There were similar morning and evening incidences of AMI in the aspirin group, in marked contrast to the placebo group which displayed the expected predominant morning peak. This leads to the question of whether there might be different mechanisms behind the morning and evening peaks[243], as aspirin appears to exert greater influence on the morning incidence compared with the evening incidence.

The activities of waking and getting up in the mornings are associated with a 20% increase in platelet responsiveness to adenosine diphosphate which may be attenuated by aspirin therapy in healthy volunteers[247]. It may be that in patients with risk factors for coronary artery disease that this platelet reactivity is even greater. This strongly suggests that at least part of the morning peak is driven by increased platelet activation.

Aspirin's anti-inflammatory properties are likely to be important as well as its anti-platelet properties. Aspirin has recently been shown to decrease circulating levels and vascular formation of soluble intercellular adhesion molecule-1, monocyte chemoattractant protein-1, tumour necrosis factor-alpha and interleukin-12p40, exerting a suppressing influence on vascular inflammation and increasing the stability of atherosclerotic plaques[261].

4.2.4 The effect of beta-blockade

The raised morning incidence of myocardial infarction appears to be attenuated amongst those who take beta-blockers prior to their infarction [242 248 255 260]. Beta-blocker therapy also leads to a diminution of the morning peak in silent myocardial ischaemia and has its major benefit in SCD reduction in post MI patients in the morning hours [124]. In contrast, patients taking calcium channel blockers still showed a morning peak, although there is a tendency to less morning infarction in patients on nitrates and calcium channel blockers, possibly due to an effect on coronary artery tone[246]. Although beta-blockers decrease the rise in pulse rate and blood pressure they do not completely abolish the circadian change in blood pressure.

Overall there is no difference in the incidence of identifiable triggers of AMI between those taking beta-blockers prior to their MI and those not. There was however a trend towards a lower likelihood of reporting physical or emotional stress as triggers ($p = 0.08$) in those on beta-blockers[254]. The effect of beta-blockers is likely to be due to a combination of effects on haemodynamics, myocardial work, and catecholamines or on platelet aggregation and coagulation.

Unfortunately, there are few data available as to whether the reduction in morning infarction seen with beta-blocker or aspirin use is due to alteration in patterns of infarction such as ST elevation or Q-wave development. However, beta-blocker therapy does not influence the incidence of morning NQWMI [262 263] and the TIMI III registry found no difference in the circadian variation in NQWMI or UA with aspirin therapy [262].

There are several possible explanations for these findings. Firstly there may be a fundamental pathological difference between QWMI and NQWMI, so that only QWMI incidence is affected. Secondly, it may be that beta-blockers and aspirin cause an attenuation of some QWMI into NQWMI, and similarly some NQWMI into UA. There is a significant amount of evidence in existence supporting the role of aspirin doing this [22a-d, 540] and this leads to further incrtimination of the platelet in the temporal pattern of ACS onset. Consequently it may be that there would be an apparent fall in the total number of QWMI, with the number of NQWMI appearing to stay the same despite beta-blockers affecting the pathology of both of them. The reason why there should be an evening peak in many studies remains unanswered. Possible psychosocial culprits include the evening meal, the journey home from work, family / marital stress and possibly a contribution from shift work patterns. The level of homocysteine undergoes natural circadian variation with a peak level in the evenings and a lowest level in the morning [264]. This may play a part in the second peak.

4.2.5 Variation in pattern of infarction – Do worse infarcts happen in the mornings?

The morning peak of AMI incidence is predominantly driven by QWMI. The Diltiazem reinfarction trial[263] found no overall diurnal variation in NQWMI, whether or not patients presented with ST elevation on their initial electrocardiogram. Gilpin et al also [248]found that NQWMI exhibited a peak in the evening only, but the TIMI III trial [262] showed only morning peak circadian variation in cases of NQWMI and UA. However patients not taking beta-blockers had a higher incidence of NQWMI in the second two quarters of the day compared with the first two. It is unclear why beta-blockade should modify the evening NQWMI rate more than the morning rate for NQWMI and vice versa for QWMI.

The TIMI II trial showed a more pronounced morning peak than the MILIS study. This may be explained by differences in their recruitment criteria, the TIMI II trial requiring ST segment elevation, rather than elevation or depression as in the MILIS trial. ST elevation is more likely to occur with occlusive thrombus, supporting the hypothesis that the morning hypercoagulable state makes ST elevation and Q wave infarction more likely to happen in the morning, as opposed to NQWMI.

The procoagulant factors discussed before (Chapter 3) which are most prominent in the morning in concert with the increased coronary tone and reactivity could be responsible for an initially non-occlusive coronary thrombus becoming occlusive, and so increasing the morning incidence of QWMI at the expense of NQWMI or UA. These are more fulyy discussed in the mechanisms section of this chapter. Inflammatory factors such as interleukins might be responsible for increased plaque vulnerability in the early morning period. The increase in haemodynamic shear stress may make major plaque rupture more likely in the morning, leading to a greater incidence of QWMI.

4.3 WEEKLY VARIATION

4.3.1 Weekly Variation in Incidence of ACS

Many studies have shown an excess of cardiovascular events on Mondays[124 243 244 253]. The Monday peak has been demonstrated in North European [253], American [265], Latin [244], and Far Eastern [266]populations. A relative trough has been seen on Saturday [243] and Sunday [253] compared with the expected number of cases. This weekend nadir in the incidence of AMI was confirmed in the analysis of 22156 patients enrolled in the CAST

(cardiac arrhythmia suppression trial) trial [265], and was also seen in an analysis of 24061 cases of SCD [259], but not all studies agree with this observation[245]. A similar pattern was seen in most subgroups irrespective of age, sex, cardiac medication and infarct characteristics (first or recurrent, Q or non-Q, site) [253].

Monday is also a peak time for SCD and ventricular arrhythmia. Analysis of information from implantable defibrillators [267] has shown an excess of ventricular arrhythmias on a Monday with a nadir on weekend days. Analysis of SCD in Scotland has shown an excess of death on Monday with less death than expected on Tuesday and Wednesday [268].

This frequency of morning infarction is greater during the working week than at the weekends (although this has not been found in all groups [269]), suggesting a superimposition of work related stress [246] on endogenous circadian rhythms. Circadian variation is found on all days of the week including weekends [243]; however the morning peak is later and less obvious on weekend days [270].

Monday incidence of AMI was noted to be less markedly raised in smokers than non-smokers in the GISSI 2 study [244]. The incidence of AMI over the course of the week was much more uniform in smokers.

4.3.2 Working Versus Retired Populations

Assessing the effect that work stress may have on the daily and weekly incidence of AMI is difficult because studies have been performed looking at populations where the non-working population are older than the working population. A bimodal pattern of AMI incidence has been suggested in the elderly [260], and so comparison with the younger

population is difficult. It may be that as people get older that they are more prone to disturbances of autonomic function and they may have different waking and activity patterns.

There is a relative risk increase of 33% towards infarction on a Monday in the working population an effect which was not seen in the retired [253]. The pattern was greater for blue collar workers than for white collar. A study of similar size also performed in Germany [243] found more pronounced increase in Monday risk in the working population, and the effect has also been seen in Japanese working men but not non-workers or working women[269]. Other studies however have shown no change in circadian or weekly rhythm with age [244]. As it seems that work stress plays a part in the increased Monday incidence in AMI then it follows that there may well be an increased risk in the working population overall.

4.4 SEASONAL DISTRIBUTION OF ACS

In Northern Europe a peak seasonal incidence of AMI and SCD has been seen in the winter months between January and March [243 255 259 265]. This is corroborated by data from 259,891 patients in the USA which showed that 53% more cases of AMI were reported in the winter compared with the summer[271]. This was true for men and women of all ages and mirrored the in-hospital case fatality rates. In England and Wales, over the winter of 1999/2000, 8% of deaths (9000 people) were attributable to the winter excess [2]. Some authors claim that patients also sustain larger infarcts as assessed by CK levels in the winter compared with the summer [272]but there is controversy about this[273].

In the Southern Hemisphere the seasonal peak of infarction occurs in their winter months of June to August, indicating that it is the season that is important and not the time of year [270]. More patients sustain infarcts on colder days in winter or summer [274] and in Kuwait, the same pattern of cardiovascular death was seen as in Scotland, suggesting that it is the relative, not the absolute temperature change which is important [275]. Even in the mild winters of Southern California there are a third more coronary deaths in the winter and this mortality correlates with temperature [276]. Ku et al examined the pattern in Taiwan, a warm sub-tropical area with little temperature variation and found no seasonal variation in the incidence of AMI[266]. Conversely some authors have noted an excess of death in very hot weather [277]and it seems likely that extreme heat can also act as an external trigger. However the vast majority of the available data support increased events during the winter time.

Kloner at al noted that the winter peak in coronary deaths was closely related to the traditional holiday period and hypothesised that overindulgence in eating and drinking and perhaps family stress at this time played a part in the pattern seen [276]. However, a winter peak in mortality is also seen in a dog model where ischaemic cardiac damage is produced by left anterior descending coronary artery ligation indicating that the holiday period is unlikely to play a major role[278].

Spielberg et al demonstrated the existence of a second peak of events in the working population [243] occurring in September. The authors hypothesised that this may be due to stresses involved in returning to work after the annual summer vacation but this is not a finding that has been replicated in other studies.

Recent analysis of malignant ventricular dysrhythmias recorded by implantable cardioverter defibrillators over an 11 year period in Germany has shown a significant seasonal peak of events in January, with the lowest incidence taking place in June [279].

Phillips et al demonstrated that there is an increase in the number of deaths in the first week of the month compared with the last week of the preceding month in a study of AMI deaths in Washington State[280]. The reason for this is not clear although the authors show a link with substance abuse, suicide, accident and homicide. It is possible that this is linked to financial stresses, as most bills and standing orders are paid at the start of the month.

4.5 POTENTIAL MECHANISMS IMPLICATED IN ENDOGENOUS ACS ONSET

4.5.1 Mechanisms affecting circadian variation

Examining the difference in patterns in different groups may provide some enlightenment about culprit mechanisms. Potential reasons for the absence of a morning peak come from examining the sub-groups involved. The incidence of morning infarction is higher in non-smokers than smokers [246]. Smokers have an attenuation of the morning peak [244 260]but preservation of the night-time nadir in incidence. Smokers have sympathetic overactivity and higher heart rates, blood pressure, coronary artery resistance and platelet aggregability compared with non-smokers. This over active sympathetic drive means that the morning increase in catecholamines may be relatively less dramatic and so the haemodynamic changes (and changes in other adrenergically driven systems) are relatively less. This may well be true for other physiological systems such as coagulation which are affected by cigarette smoking. Consequently the relative

morning physiological changes are less and this may explain the lower morning peak. Smokers also have a lower morning peak on Mondays [244]suggesting that the same mechanisms underlie the morning and the Monday increases in incidence. The heightened sympathetic tone throughout the whole day in these groups may play a part in the overall increased risk seen [244], and it suggests that the change in sympathetic drive may be responsible for part of the morning peak in circadian variation.

Diabetics also demonstrate blunting of the normally observed circadian rhythms [260] and show absence of the usually observed seasonal rhythms [255] with no peak times of incidence. Diabetics may produce less of a catecholamine and haemodynamic surge because of autonomic neuropathy, reinforcing the role of the autonomic nervous system in the pathogenesis of triggering.

Several studies have suggested an attenuation of circadian variation in patients with previous myocardial infarction [248 255], but this has not been found in all studies [281]. There is derangement of sympathovagal rhythms in patients with previous infarction and so it is a possibility that this group may have a different pattern of incidence from first time infarcts. Gilpin et al found that patients with previous infarction had a greater incidence of QWMI in the morning followed by an increase in the incidence of NQWMI later in the day, thus showing no overall peak [248].

This sympathovagal balance may be especially important in the alteration seen in the patterns of circadian variation in patients with diabetes mellitus. Autonomic and ambulatory ischaemia testing in diabetes have yielded interesting information on the role of the autonomic nervous system in myocardial ischaemia. Diabetics with autonomic neuropathy do not demonstrate the morning peak seen in ambulatory ischaemia whereas

diabetics with intact autonomic function did show this peak [281a]. Sympathetic dominance has been seen in studies of diabetics and is related to pancreatic beta-cell function [281 b-d.] This imbalance of autonomic tone has also been seen in studies of acute mental stress [281e] and demonstrated in studies of heart rate variability [587]. As discussed elsewhere, the multiple effects of the sympathetic nervous system on heart rate, vascular tone as well as coagulation factors and platelets makes it a theoretically culpable and potentially pivotal linking mechanism between psychosocial factors and the manifestations of atherosclerotic cornary artery disease.

Depression is associated with an increased incidence of CAD and with abnormalities in several biochemical, haematological and immune parameters as well as some circadian rhythms [282]. Depressed patients have the highest rate of infarction between 22.00 and 06.00 in converse to the usual pattern seen, but there was a high incidence of smoking in this study population that may have affected results[283]. The role of acute depression or depressive symptoms and onset of ACS is still unclear.

There may be a cultural contribution to the pattern of infarction. The World Health Organisation studied patients from 19 different countries [270]and found an overall morning peak of AMI incidence. However looking at the individual countries separately there is a wide variation in peak times of incidence which may relate to cultural differences in rising, working, dining and social habits.

Several physiological functions undergo a natural circadian rhythm that may lead them to act as acute risk factors and predispose to morning infarction. These probably work in combination to give the ultimate effect. On waking there is a surge in catecholamine and cortisol levels and a rise in both blood pressure [249 284] and pulse rate that could increase

shear stresses across atherosclerotic plaques. There has been recent interest in different gene polymorphisms such as the angiotensin converting enzyme gene, and this has been shown to alter the circadian pattern of blood pressure[285]. It may be that other polymorphisms are identified which play a role in the triggering of acute coronary events.

Vascular tone increases causing a rise in systemic vascular resistance and increasing cardiac work predisposing to ischaemia. An increase in coronary arterial tone [286] reduces blood flow across atherosclerotic lesions. There is increased blood viscosity and factor VII activity in the morning while endogenous fibrinolytic activity is low and platelet aggregability is higher [247] leading to a hypercoagulable state [7]. This is manifested by the circadian variation in the resistance to thrombolytic treatment with morning and late evening peaks in resistance [258]. A large number of studies have now shown diurnal variation in factors such as native tissue plasminogen activator, plasminogen activator inhibitor, von Willebrand factor antigen all contributing to an increase in endogenous coagulability in the morning [286a-f.]

Cytokines also show circadian variation with interleukin-6 displaying a morning zenith at about 5 to 6 am and a nadir at 08.00 to 10.00[287] [288]. This may predispose to a pro-inflammatory state in the very early morning period. Whereas the rise in cortisol is governed by the time, other factors such as platelet aggregability are linked to the adoption of the upright posture on rising in the morning [247]. It is likely to be the individual's own daily activity cycle that is important rather than the absolute time of day. There may also be interaction between different components of the circadian cycle, for example, assumption of the upright posture may be more likely to cause intense vasoconstriction when endogenous cortisol levels are high.

Recently there has been interest in the circadian variation in vascular endothelial function. In patients with CAD, coronary segments with dysfunctional endothelium exhibit an early morning exaggeration in basal tone as assessed by response to acetyl choline and to nitroglycerine [289]. There is a circadian difference in endothelial dependent flow mediated dilatation with maximal dilatation occurring in the afternoon and attenuation in the morning [290 291]. Otto et al demonstrated marked decrease in endothelial dependent flow mediated dilatation in the early morning after waking (6 a.m.) which recovered by late morning (11 a.m.). The flow mediated dilatation was only 4.4 +/- 0.7% at 6.a.m. which increased to 7.7 +/- 1% at 11a.m. and 7.5% +/- 1% at 9 p.m. [292]. There was no difference in endothelial independent flow at these times. These times correspond with low and high levels of endothelin-1 (a potent vasoconstrictor) which also undergoes a circadian variation. This may enhance the expression of adhesion molecules and leucocyte adhesion with peaks at 08.00 and 20.00 and a nadir at 16.00[290]. In areas with endothelial dysfunction there might be impaired opposition to the alpha-adrenergic constricting stimulus of the morning sympathetic surge because of impaired production of nitric oxide as a local vascular dilator. The increase in reactivity may cause an increased morning predisposition to coronary artery spasm. Levels of melatonin, a pineal hormone that has a circadian variation, have also been demonstrated to be lower in patients with unstable coronary syndromes compared with patients with stable symptoms or normal controls[293]. Other factors have been proposed that may play a role in the morning incidence of infarction such as the sleep apnoea syndrome [294].

Morning is the time of peak number of circulating polymorphonucleocytes and both soluble intercellular adhesion molecule-1 (sICAM-1) and E-selectin show a nadir at around 04.00 and a level rising over the course of the morning to a peak at 12.00[295].

Thus, the morning period has increased leukocyte and endothelial activation, and there may be an alteration in the inflammatory balance at this time favouring inflammation and plaque instability as well as a pro-atherogenic environment.

Other factors may contribute to a prothrombotic state such as the circadian expression of CLIF (cycle like factor) which helps regulate expression of the plasminogen activator inhibitor complex (PAI-1) gene in endothelial cells [296]. Patients with morning infarction have elevated levels of lipoprotein (a) (Lp(a)) (which has been linked to the acceleration of atherosclerosis) and of thrombin-antithrombin III complex, with a positive correlation between Lp(a) and PAI-1 and a negative correlation between Lp(a) and t-PA[297].

A circadian variation has been demonstrated in WBC aggregation in men with CAD. The largest rise in WBC aggregation was seen between 08.00 and 12.00; and this may predispose to thrombosis via effects on platelets and red blood cells. There is also increased free radical production in patients with CAD, and whereas healthy volunteers have a fall in free radicals in the morning, patients with CAD have persistently elevated levels and low levels of free radical scavengers[298]leading to potentially greater oxidative stress.

Electrocardiographic parameters also alter over the course of the day. There is maximal variability in the QTc interval on the ECG in the morning which is likely to reflect a state of autonomic instability and may be linked to the increased incidence of SCD [299].

Circadian variation in the above factors could lead to increased incidence of plaque rupture in the morning. It could be that plaque vulnerability is a random occurrence and the morning peak of infarction is due to greater plaque rupture with the haemodynamic

and sympathetic surge. Conversely it could be that increased plaque inflammation and friability makes plaque rupture more likely from within the plaque itself or more vulnerable to external forces. There is likely to be a combination of increased intrinsic plaque susceptibility acted upon by increased haemodynamic stresses, superimposed on a prothrombotic milieu.

4.5.2 Mechanisms affecting weekly variation

Whereas time of day, months and seasons are influenced by natural events (the solar cycle, lunar cycle and earth's orbit), Monday is a completely artificial construction. This association of Monday with increased myocardial infarction and sudden cardiac death lends considerable weight to the theory that mental stress and particularly work stress is involved as a triggering factor or a contributing factor towards plaque instability or infarction. This could be due to the increased stresses of returning to work on Monday compared with the relative rest of Sunday. The relative paucity of deaths on a Tuesday compared with Monday may be related to the triggering effect of a Monday causing rupture of the most vulnerable plaques leaving more stable ones behind. Unfortunately there are no data available on the effect of beta-blockers or aspirin on the daily incidence of ACS.

A study of blood pressure measurement in general practice has shown a higher blood pressure on Mondays with the lowest value being on Fridays. There was also a correlation between magnitude of blood pressure and the amount of alcohol consumed over the weekend period [300].

4.5.3 Mechanisms affecting seasonal variation

A U.K. study showed no seasonal rhythm in South Asians, diabetics or those taking aspirin or beta-blockers on admission[255]. The fact that over 40% of the South Asians in this study were diabetic and thus prone to autonomic function disturbance possibly explains the loss of circadian and seasonal variation observed, with the variation being due to diabetic autonomic disease rather than being of South Asian origin. The fact that similar groups display a loss of circadian and seasonal rhythms raises the question of whether the same mechanisms are involved in the two phenomena. More patients sustain infarcts on colder days and so relative temperature appears to be important [274].

Various other factors have been suggested as the cause of increased mortality in the winter months. These include fewer hours of sunlight, higher fibrinogen levels, lower fibrinolytic activity, and higher plasma cortisol levels, haematocrit and granulocyte levels in the winter [243]. Temperature levels seem to be especially important as a reduction in winter cardiac death is seen in better heated homes [2]. Blood catecholamine levels rise in exposure to cold and increased sympathetic activity in the winter may be the cause of the seasonal variation seen [255]. Some authors have hypothesised that the reduced hours of daylight time are sensed by the supra-chiasmatic nucleus, and that this alters the circadian clock and affects neurophysiological and sympathetic nervous outflow. Other suggestions for the winter increase in ACS have been increased respiratory infections acting as inflammatory triggers and increased particulate air pollution from increased fuel burning [276].

Vascular tone is likely to play a significant part in the increased rates of SCD seen in the winter. Increased tone leads to increased afterload and increased myocardial work and oxygen consumption making coronary ischaemia more likely [279].

4.6 CONCLUSIONS

There is compelling evidence to show that there is an increased incidence of coronary events in the mornings, on Mondays and in winter. There is strong evidence for the existence of a second peak later in the afternoon, but some controversy remains regarding the pattern seen in some sub-groups. Alterations in the normal patterns seen in some patient sub-groups give us insight into some of the potential underlying mechanisms, especially implicating the sympathetic nervous system. It is interesting to note that stroke also follows a similar circadian, weekly and yearly pattern [301 302]. There is some data weakness, as most of the information we have has come from post hoc analysis of studies set up to look at other variables than timing of infarction. Better information could be gleaned from a specifically designed and powered epidemiological study.

It is likely that an interaction of several factors is responsible for the patterns seen. The interactions between the sympathetic nervous system, blood coagulation and coronary artery tone are likely to be especially important. Other factors such as the effects of genetic polymorphisms, endothelin, endothelial function, adhesion molecules, free radicals and interleukins have still to be fully evaluated. There may be different balances in the influence exerted by individual factors resulting in the differing sub-group patterns and in the difference between the morning and evening peak.

There is enormous scope for future investigation and research, and it will be exciting to see how substances like adhesion molecules and matrix metalloproteinases fit into this scheme and whether they may lead to new therapeutic discoveries. This identification of risk periods allows targeting of therapies to cover the time of highest risk and also

identification of high-risk groups who may benefit most from therapy. Similarly, if triggers can be identified then it may be possible to modify these and so reduce the death rate from ischaemic heart disease.

Chapter Five

PSYCHOSOCIAL TRIGGERS OF ACUTE CORONARY SYNDROMES

5.1.1 INTRODUCTION

The notion that emotions and behaviours trigger cardiac events in susceptible individuals has a long history. There are many anecdotal reports of factors such as physical and mental stress acting as triggers for acute coronary syndromes (ACS). One nineteenth century physician observed that sudden cardiac death (SCD) might follow "Playing Hamlet, or holding the breath during a military flogging" [303]. Famous cases can be cited, such as the surgeon John Hunter who collapsed and died during a heated meeting at St. George's Hospital. Hunter had advanced coronary atherosclerosis, and his death was almost certainly cardiac in origin, notwithstanding the myth concerning syphilis first propounded by D'Arcy Power [304]. More recently, the scientific literature concerning the triggering of acute coronary syndromes (ACS) has developed considerably over the past 15 years[305].

This chapter examines the current state of knowledge regarding psychosocial (psychological, behavioural, physical and environmental) triggers of ACS critically assessing findings in the light of study designs and the methodological difficulties of evaluating these associations. Secondly, the evidence concerning triggering is linked with the pathophysiological processes implicated in ACS, focusing on plaque vulnerability and the 'vulnerable patient' [15 20].

5.1.2 What is a trigger?

A trigger has been defined as an external stimulus or activity of the patient that produces acute physiological or pathophysiological changes leading directly to onset of acute cardiovascular disease[305]. There is no general agreement on how long before the onset of symptoms an activity can take place to be regarded as an acute trigger rather than a more general aetiological factor. Studies typically assess activities in the period ranging from a few minutes to 24 hours before ACS onset. Most recently attention has focussed on a 1 to 2 hour period before the onset of symptoms.

Triggering is a phenomenon that can only be identified retrospectively. This makes measurement susceptible to biases such as recall and social acceptability bias, and to patients' private beliefs about the causes of heart disease. It also makes analysis of triggers of fatal cardiac events difficult, unless the incident was witnessed by others. It is possible that the triggers of fatal events are different from those described in the literature on non-fatal ACS.

The ability of psychosocial factors to act as a trigger for ACS depends on the existence of a vulnerable atherosclerotic plaque, this concept of plaque and patient vulnerability has been discussed in chapter 2.

5.1.3 Pathophysiology of ACS

Any factors which predispose to plaque disruption and the way in which these factors are further modulated by psychosocial factors is therefore important. For example, emotional and behavioural stimuli that elicit an acute increase in vascular inflammatory factors (such as proinflammatory cytokines, platelet activation, and adhesion molecules), or cause episodes of high haemodynamic shear stress may stimulate plaque disruption, and so factors inducing acute increases in heart rate, blood pressure, myocardial oxygen demand and vasoconstriction are all relevant.

It is evident from histological studies that episodic plaque rupture is a frequent event that only occasionally results in an ACS [306]. Imaging studies using intravascular ultrasound have shown that ACS patients have lesions with all the features of plaque rupture at multiple sites that are distant from the culprit lesion [307]. It is important to consider not only what precipitates plaque rupture but also what factors influence physiology after plaque rupture to transform it from a silent to a clinically meaningful episode. Evidence of this type has led to the conclusion that two other factors apart from rupture itself need to be taken into account. The first is the presence of procoagulatory and antithrombotic factors in the blood. After a plaque rupture, the local balance between prothrombotic and thrombolytic factors will determine whether vessel occlusion takes place and if so, to what extent. Increased levels of fibrinogen, D-dimer and clotting factors, and reduced endogenous fibrinolytic activity, are relevant in the acute phase. The second factor is the presence of a myocardium that is susceptible to ischemia [20]. Autonomic processes strongly influence outcome after plaque disruption, with sympathetic hyperactivity provoking potentially life-threatening ventricular tachyarrhythmias, while vagal activity

is protective [308]. In cases of SCD without thrombosis, coronary spasm may be particularly relevant.

There are consequently several steps in the ACS process where psychosocial factors may modify pathophysiology to alter the clinical course. Firstly there is the role in the initial development of atherosclerosis as discussed in chapter 3. Secondly there is their involvement in the existence of the state of patient / plaque vulnerability. There is then not only the trigger stimulus for plaque rupture but also the influence upon factors which affect the severity of intravascular thrombosis and vessel occlusion. There are also factors which may affect the electrical stability of the myocardium and its predisposition to dysrhythmia.

An important consequence of these pathophysiological processes is that triggers could operate in two ways. The first possibility is that triggers cause ACS in patients who would have suffered a cardiac event in the very near future anyway, harvesting highly vulnerable plaques through rupture or erosion. The second possibility is that triggers cause ACS in patients who would otherwise have remained stable, by stimulating the combination of inflammation, procoagulatory responses and autonomic imbalance. In such cases, the trigger may not cause plaque rupture or erosion, but rather affect the milieu in which the rupture takes place, ensuring that it is followed with sufficient thrombosis or ventricular instability to promote a clinical cardiac event.

The implications of these two possible scenarios are significant clinically. If triggers act only on very vulnerable patients, the concept of 'brought forward time', borrowed from fields such as the study of air pollution in asthma and life events in psychiatric research, becomes relevant. Brought forward time is the period that would otherwise have elapsed

before the manifestation of the ACS, had a trigger not been present. For example, in population studies, the high incidence of ACS following a particular trigger may be followed for some days by a period of low incidence of ACS, since vulnerable plaques will already have been harvested by the trigger.

5.2 PSYCHOSOCIAL TRIGGERS

Psychosocial triggers have been investigated using two main approaches: studies of public events, and clinically-based studies of personal experiences. Public event studies involve stimuli such as earthquakes, war, or exciting sporting occasions. The advantage of studying such stimuli is that the triggering event and its timing can be identified objectively, a population-based sampling frame can be utilized, and fatal as well as nonfatal cardiac events can be evaluated. A population perspective also permits an evaluation of brought forward time hypothesis, since a high incidence of ACS following a public event or natural disaster might be followed by a period in which relatively few ACS occur. Very often, however, the circumstances surrounding natural disasters or conflict are not conducive to rigorous data collection, and most ACS take place in individuals who are not exposed to large scale traumatic events.

Studies of personal experiences such as physical exertion or emotional stress are more common. Unfortunately, triggering is a phenomenon that is difficult to investigate prospectively, so data collection is typically retrospective, and susceptible to memory loss, social acceptability bias, and to patients' private beliefs about the causes of heart disease. Clinical studies of the triggering of fatal cardiac events are difficult, unless the circumstances are witnessed by others. It is possible that the triggers of fatal events are different from those described in the literature on non-fatal ACS. The majority of work

published to date has examined acute myocardial infarction (MI) and SCD, with little research on unstable angina.

5.3 THE OVERALL INCIDENCE OF TRIGGERS

Several large-scale studies in the early 1990s evaluated the incidence of triggers of AMI by interviewing patients soon after their hospital admission. These studies have differed in their methods, measures and the interval between symptom onset and assessment of triggers, and this may account for the wide differences in the prevalence of possible triggers that have been reported. Many of the studies reporting triggers were clinical trials designed to assess treatment efficacies rather than triggering specifically and examination of triggers has been done as post-hoc analysis.

The Multicenter Investigation of Limitation of Infarct Size (MILIS)[254] study interviewed 849 AMI patients within 18 hours of symptom onset, of whom 48.5% reported a possible trigger. Emotional upset (18.4%) and moderate physical activity (14.1%) were the most common triggers, followed by lack of sleep and overeating, and 13% described multiple possible triggers. The pilot phase of the Triggers and Mechanisms of Myocardial Infarction (TRIMM)[245] study involved 224 AMI patients who were interviewed an average of 16.8 days following admission. 67% reported possible acute triggers, with 52% reporting either emotional upset or stress within the 24 hours preceding infarction. By contrast, only 10% of 1,818 patients in the Secondary Prevention Reinfarction Israeli Nifedipine (SPRINT) study reported possible external triggers of AMI [309]. Exceptionally heavy physical work, violent quarrels and stress at home were the most commonly mentioned triggers. In a sample of 1,480 patients with anterior or inferior AMI admitted to hospital in Split, Croatia, the frequency of triggers was 44%, with exercise, emotional

stress, cold and wet weather, and overeating being most common [310]. Other large scale studies such as Determinants of Myocardial Infarction Onset (Onset) Studies, [115 311-315], the Thrombolysis in Myocardial Infarction phase II (TIMI II) study [246]and the onset study within the Stockholm Heart Epidemiology Program (SHEEP) [316 317]have also interviewed large samples of patients soon after admission; however, they have not presented the overall incidence of triggers, but rather the occurrence of specific types of trigger events, as detailed later in this chapter.

Younger patients, non-diabetics and men were more likely to report triggers in the MILIS, SPRINT and the Croatian studies[254 309 318]. In the MILIS study, there was no significant difference in the identification of triggers for Q wave myocardial infarctions (QWMI) versus non-Q wave (NQWMI), or regarding angiographic severity of coronary artery disease[254]. Culic et al however noted that external trigger factors associated with AMI led to a greater incidence of QWMI [318]. There was no difference between the identification of trigger factors for infarcts occurring in the morning compared with the afternoon.

Triggers are more common during the daytime hours of 6.00 a.m. to 6.00 p.m. than in the evening / night-time between 6.00 p.m. and 6.00 a.m.[245]. The MILIS study identified no link between site of infarction and triggers but Miric et al [310] noted a tendency for inferior compared with anterior wall infarcts to be associated with triggers, notably emotional stress, cold and wet weather, overeating within the past hour, and greater than usual smoking levels. By contrast, anterior wall infarcts were associated more consistently with physical exertion. This finding has not been replicated by others.

The MILIS study showed no overall difference in triggering between those taking beta-blockers within the 3 weeks prior to their infarction and those not taking beta-blockers. There was however a trend towards a lower likelihood of reporting physical or emotional stress as triggers (p = 0.08) for patients taking beta-blockers suggesting a role for the sympathetic nervous system in the aetiology of these triggers [254]. Beta-blocking drugs have also been shown to attenuate the circadian and seasonal peaks of acute coronary events [319].

5.4 LIMITATIONS TO INTERPRETATION OF RESULTS

Two major problems limit the interpretation of studies that simply enquire about the occurrence of triggers. The first is patients' reports may be influenced retrospectively by their attempts to make sense of their predicament. Studies of illness representations indicate that patients develop causal models of heart disease, with stress and physical activity featuring high on the list of presumed causes [320]. By the time that individuals are interviewed, these views may be established, and will influence responses to enquiries about the triggering period. The second problem is that control groups or control time periods are not tested. Physical exertion, emotional stress and other factors may occur frequently in patients' lives, so their association with the onset of ACS may be coincidental. Case-control methods can be used, but as Maclure and Mittleman [321] have pointed out, there are difficulties in identifying appropriate control groups. General population controls have the limitation not only that healthy individuals will be most likely to participate, leading to a healthy volunteer bias, but also that people will be less likely to agree to be assessed on a stressful day. These factors may bias the comparison. Data from individuals hospitalized for other emergencies can be used, but will be compromised by whatever caused their medical problems.

The investigators in the Onset study therefore developed the case-crossover design, in which the critical time periods are compared with control time periods on a within-subject basis so effectively the patients act as their own controls[321 322]. This method involves questioning patients about potential triggers during the hazard period, and then for control periods. For example, an ACS patient might be questioned about emotional stress in the 2 hours preceding symptom onset, and then about the corresponding 2 hours that occurred 24 hours earlier, or another time period such as the last week or the previous 6 months. If a patient is habitually emotionally stressed, then he or she will report stress for both time periods. By comparing hazard and control periods, the relative risk that an episode of emotional stress is followed by an ACS can be calculated. This method has many advantages in the analysis of transient exposures, since self-matching eliminates selection and individual reporting biases. Any difference in chronic cardiovascular risk profile between cases and controls is eliminated, reducing the risk of residual confounding. Several of the results described in this review have used this method. Nonetheless, it does have limitations, and these are detailed in a later section.

5.5 ENVIRONMENTAL TRIGGERS OF ACS

5.5.1 Temperature

Extremes of both hot and cold temperature have been associated with an increased risk of cardiovascular death. In an analysis of winter blizzards in Massachusetts between 1974-1978, deaths from ischaemic heart disease rose by 22% and accounted for over 90% of the excess mortality [323]. There was a greater effect seen in males than in females, and the effect persisted for eight days after the blizzards, potentially linking deaths to

activities such as snow shoveling. There is not only increased AMI in winter, but also on cold days independent of season [274].

Various factors have been suggested as the cause of increased mortality with exposure to cold. These include temperature, hours of sunlight, lower fibrinolytic activity, and higher plasma cortisol, haematocrit and granulocyte levels in the winter [243]. Blood catecholamine levels rise on exposure to cold [324], and increased sympathetic nervous system activity in the winter could also be a contributory factor [255].

Conversely, during a record heat wave in Chicago in 1995[325] there were at least 700 excess deaths. Among persons with pre-existing heart disease, there was an odds ratio of 4.5 of experiencing cardiac death at the time of the heat wave. In Philadelphia, there was a heat wave in 1993 which was associated with a 98% increase in cardiovascular deaths [326]. As recently as 2003 there was a major heat wave in France which caused the death of an estimated 15000 people, deaths were reportedly more likely in the elderly, those with pre-existing cardiac or respiratory disease, renal failure or mental illness. Most of the deaths were due to cardiac death [327].

Exposure to extreme heat causes severe dehydration and cardiovascular collapse with an initial rise in pulse and stroke volume with a decrease in vascular resistance. Heat stroke is able to induce cellular hypoxia and metabolic stress in visceral organs [328], and this may also be relevant to the heart. Heat stroke is accompanied by an inflammatory response with a rise in interleukin 6 (IL-6) and IL-1 as well as tumour necrosis factor (TNF) [329], which may contribute towards triggering acute events in patients experiencing extreme heat.

5.5.2 Infection

Several bacteria and viruses (in particular, *Chlamydia pneumoniae, Cytomegalovirus, Helicobacter pylori*) have been associated with CAD although definitive proof is lacking. Infectious agents could play a part in two ways. They could cause an inflammatory response in the blood vessel acting as a stimulus for atherogenesis, or they could institute an inflammatory state with cytokine release and subsequent plaque weakening and rupture leading to an acute coronary event. The data regarding *Helicobacter pylori* is seriously confounded by socio-economic class, and meta analysis of the data and a subsequent prospective study [330] [331] have shown no definite link. *Cytomegalovirus* similarly has been reviewed and is unlikely to be a strong risk factor for the development of acute myocardial infarction [332]. The bulk of the evidence relates to *Chlamydia pneumoniae* (*C. pneumoniae*), but even then there have been both positive and negative studies. Acute infection leading to an inflammatory response seems a very plausible precipitant of acute coronary events but at the moment there is no conclusive evidence that *C. pneumoniae* either causes atherosclerosis or precipitates acute events [333]. The failure of recent trials of antibiotics designed to treat *C. pneumoniae* to reduce recurrent ischaemic events in patients with ACS casts further doubt on the role of acute infection in triggering [334] [335]. One recent study has reopened the debate on infectious precipitants [336]. The incidence of hospital admission for cardiac disease in a cohort of over 140 000 elderly patients receiving influenza vaccination was compared with controls and a 19% reduction was seen in the vaccination group, but the difference specifically for AMI was not reported. However this finding has not been seen in other studies [337].

5.5.3 Air Pollution

Exposure to high levels of particulate air pollution is associated with an increase in cardiovascular mortality [338 339]. Increased hospital admissions for cardiovascular disease has been seen on days when levels of PM10 (particulate matter less than 10 micrometers in aerodynamic diameter) are highest [339]. In a sub-study of the Onset study, an increased environmental concentrations of fine particulate matter was associated with elevated risk of AMI over the following two hours [338]. There was also a delayed effect associated with exposure in the preceding 24-hour period. Other pollutants such as black carbon, nitrogen dioxide and sulphur dioxide showed positive associations. A recent Italian case crossover study of AMI showed positive associations between particulate matter, NO2 and CO and admission for AMI. The association was strongest in the elderly and on warm days [340].

Exposure to air pollutants leads to several events that could potentially trigger ACS. It has been hypothesised that particulate air pollution could cause an inflammatory response, and increased levels of C-reactive protein (CRP) have been seen in healthy men after exposure [341]. There is local cytokine production, systemic hypercoagulability and increased plasma viscosity [338 341]. A haemodynamic response is also evident, with increased heart rate, decreased heart rate variability and arterial vasoconstriction as well as ECG ST-segment changes seen in experimental models [342]. The risk of developing ischaemia on exercise treadmill testing is increased after exposure to increased environmental levels of fine particulate air pollution [343]. Also, a study of 100 patients with implanted cardioverter-defibrillators showed a direct association between defibrillator discharges and increases in atmospheric nitrogen dioxide over the previous two days [344].

5.6 PHYSIOLOGICAL TRIGGERS

5.6.1 Physical activity

Physical exertion has an apparently paradoxical association with the triggering of ACS; people who are habitually physically active are at reduced risk, but vigorous activity has been found acutely to trigger both MI and SCD. The proportion of patients who reported moderate or vigorous physical activity prior to acute MI was 23% in the MILIS study, 18.7% in TIMI-II, and 27.1% in a case series in New Zealand [246 254 345]. The levels of heavy exertion prior to acute MI were 4.4% in the Onset study [311] and 7.1% in the main TRIMM study in Augsberg, Germany [346]. Using case-crossover methods, the relative risk of having engaged in vigorous activity in the hour prior to cardiac events has been estimated at 5.9 (95% confidence interval 4.6 to 7.7) and 2.1 (C.I. 1.6 to 3.1) in different samples [346 311]. In the SHEEP study, the relative risk was 3.3 (C.I. 2.4 to 4.5) for physical exertion in the hour preceding acute MI, but this increased to 6.1 (C.I. 4.2 to 9.0) in those who had no premonitory symptoms.

There is also a strong protective effect of regular exercise. In the Onset study, the relative risk ranged from 2.4 in those who exercised five or more times per week, to 107 in those who exercised less than once a week [311]. In the TRIMM cohort, the relative risk was 6.9 among those who exercised fewer than four times a week, compared with 1.3 for those who exercised above this level [346].

Vigorous activity is a trigger for SCD as well as nonfatal events. Physical activity is more likely to induce dysrhythmia and induce defibrillation from ICDs than control

periods [347]. An analysis was carried out of deaths in the Physician's Health Study, using case-crossover comparisons with habitual exercise levels measured previously by questionnaire[348]. Of the 122 SCD recorded over a 12 year period, 23 were preceded by vigorous exertion within the previous 30 minutes. The relative risk was 16.9 (C.I. 10.5 to 27.0), but ranged from 10.9 (C.I. 4.5 to 26.2) in those who exercised regularly to 74.1 (C.I. 22.0 to 249) in those who were sedentary. These findings are corroborated by a case-control analysis of SCD during downhill skiing, in which risk was substantially greater among men who were not habitually active [349].

These studies therefore show a consistent pattern, despite the variation in relative risks. Whereas it seems that frequent exercise has a protective effect, sudden heavy exertion in otherwise sedentary people is a potent risk for myocardial infarction. Although the relative risk of both AMI and SCD rises with vigorous exercise, the absolute risk is very low. In the Physicians' Health Study, it was estimated that the absolute risk following any individual episode of physical activity was one death per 1.51 million episodes.

Physical activity is a more common trigger in men than women in some [254 318] but not all studies [346 350]. This may be in part because middle-aged men engage in more leisure-time physical activity than women. There is some difference in the clinical risk profiles in patients who present with exertionally triggered ACS. Patients with exertion associated AMI are generally younger, have fewer cardiac risk factors and take fewer cardiac medications than other patients [311 345]. Being white, normotensive, obese, or having had no angina in the preceding 48 hours were independent predictors of AMI beginning during physical activity[351 246 345]. There is no difference in diabetic status between exercise and rest-onset infarctions[345 351]. The effect of smoking and hypercholesterolaemia has been variable [246 345 351]. In the SHEEP study [350] it was found

that the risk associated with vigorous exertion was greater in manual workers compared with patients of higher socioeconomic status.

Some studies have shown that patients with exercise-onset AMI tend to have less advanced coronary artery disease. At coronary angiography, patients with exercise-onset AMI are more likely to have either no significant angiographic coronary stenosis or to have occlusion of the infarct related artery than patients with rest onset infarction[246]. Giri et al found a greater incidence of single vessel disease and of thrombus in the infarct-related artery in patients who had exercise induced AMI [351]. Patients with exercise-onset AMI also had greater diameter of their infarct-related artery, probably reflecting less severe atherosclerotic disease [351]. This less advanced coronary artery disease may explain why patients in a case series from New Zealand (after adjusting for age and gender) with exertion-onset infarction had significantly lower in-hospital mortality and risk of heart failure than those with onset in bed [345].

The additional haemodynamic change associated with exertion may cause rupture of previously non-significant plaques. An autopsy study comparing men who died suddenly during strenuous physical activity or when at rest showed plaque rupture in 72% cases of exertion-induced SCD compared with 23% of those dying at rest, and haemorrhage into the plaque was also frequent [352].

Myocardial ischemia during exercise testing is of course a common phenomenon, and physical activity also triggers ischemia during everyday life in patients with coronary artery disease [353]. Using case-crossover methodology for analyzing electrocardiographic (ECG) ischemia during ambulatory monitoring of patients with coronary artery disease,

Gullette et al [354] reported a relative risk of 13.2 (C.I. 7.4 to 23.6) for heavy physical activity in the hour preceding onset, after adjusting for time of day. Both ischemia on treadmill testing and ambulatory ECG ischemia predict cardiac events prospectively [355].

Several mechanisms implicated in ACS may be triggered by physical exertion. Physical activity elicits an acute increase in sympathetic activity and release of catecholamines. The weighting of autonomic activity in favor of the sympathetic over parasympathetic tone leads to cardiac electrical instability and risk of ventricular fibrillation [308]. The haemodynamic change associated with exertion may cause rupture of previously non-significant plaques if vulnerable. The catecholamine response to exercise stimulates surface expression of adhesion molecules, and there is a pronounced rise in the concentration of interleukin 6 (IL-6) in the circulation [356]. Physical exertion stimulates both coagulation and fibrinolytic pathways, and there is some evidence that more intensive activity tips the balance towards procoagulatory responses [357]. Patients with coronary artery disease may also have greater coagulation potential than healthy individuals, due in part to resting differences in plasminogen activator inhibitor-1 levels (PAI-1) [358]. Exercise increases platelet aggregability in patients with CAD [359]. Beta-blockers or aspirin have a protective effect upon exercise-onset infarction [345 351]. Habitual leisure-time physical activity is, by contrast, associated with lower resting levels of inflammatory markers such as C-reactive protein and soluble intracellular adhesion molecule-1 (sICAM-1), lower plasma viscosity and haemostatic factors such as D-dimer, von Willebrand factor, and increased levels of tissue plasminogen activator (t-PA), fibrinolysis and tissue plasminogen activator (t-PA) [360-362].

Knowledge about training effects on haemostatic factors is limited, but there is evidence that training has beneficial effects on platelet activation and aggregation [357]. The acute effects of physical activity on vascular endothelial function have not been clearly established [363], but endothelial function can be improved in normal subjects [364] and patients with coronary artery disease by exercise training [365]. Physically fit people show a lower rise in diastolic blood pressure and pulse rate than unfit people [366]. Fitter people also report less anger and anxiety than their unfit peers.

It is important to bear in mind that physical activity may coincide with periods of acute mental stress, especially in traumatic conditions (natural disasters, assault etc). Depression is inversely associated with physical activity [186]. It is possible that people under stress or suffering from depression are less likely to exercise regularly and so would be more at risk from the effects of sudden unaccustomed physical exertion.

5.6.2 Sexual Activity

The role of recent sexual activity as a trigger of acute MI has been studied in both the Onset and SHEEP studies, with similar results. In the Onset study, sexual activity was reported within two hours of MI by 3.0%, with a relative risk using the case-crossover method of 2.5 (C.I. 1.7 to 3.7)[367]. In the SHEEP study, 1.3% reported sexual activity over this time period, with a relative risk of 2.1 (C.I. 0.7 to 6.5) [317]. However, as absolute rates of infarction were low, there was in reality an extremely small risk of infarction being triggered by sexual activity (estimated at one chance per million people per hour). In both studies, risk was greater in patients who were sedentary, suggesting that the mediating mechanisms may be similar to those operating with physical exertion.

Studies using ambulatory ECG monitoring indicate that heart rate increases to 118 – 127 beats per minute during sexual intercourse [368 369]. In a study of 88 men with documented coronary artery disease, ECG signs of myocardial ischemia occurred in 31% during sexual intercourse, and in 78% of these individuals, ischemia was silent (asymptomatic) [368 369]. One early Japanese study of SCD during sexual activity stated that 75% of cases occurred during extramarital sex with a younger partner, but the generalisability of this finding is unclear [370].

Sexual activity is often carried out as part of a loving intimate relationship. Since social support and good marital relationships are strongly protective for cardiovascular and other health endpoints [371 78], the benefits of sexual activity may offset the quite small risks. The mechanisms behind sexual activity as a trigger are likely to be similar to physical activity although there may be a greater degree of autonomic arousal involved.

5.6.3 Menstrual Cycle

669 women were interviewed as part of the Onset study, of whom 3.1% were still experiencing menstruation [315]. The women involved were generally young, white and parous, with a high incidence of cigarette smoking and obesity. The early follicular phase of the menstrual cycle was associated with a three-fold increase in risk of symptom onset for AMI compared with other times in the cycle. Oestrogen levels have been found to correlate with flow-mediated brachial artery endothelial function and to have a negative correlation with ischaemic episodes in women with variant angina [372].

5.6.4 Sleep Disturbance

A substantial number of cases of ACS and SCD occur during the night when patients are asleep. Sleep is associated with dynamic changes in autonomic tone, neuroendocrine function and inflammatory cytokine release. The occurrence of cardiac events during sleep is also not uniform, with a high frequency of acute MI, SCD, and discharge from implantable cardioverter-defibrillators early in the night, followed by a trough before waking [373]. Whether there are triggers for ACS in the night is not known.

Lack of sleep was identified as a possible trigger for AMI by about 8% of patients in the MILIS study [254]. It was more frequently identified by patients less than 50 years old. When triggers were studied in combination, the commonest combination was lack of sleep and emotional upset.

Disturbed sleep is associated with disturbances of cortisol output and hypothalamic-adrenocortical function with compensatory increases in sympathetic tone and cortisol output in the evening [374]. Chronic insomnia is associated with a shift in the pattern of IL-6 and tumor necrosis factor α (TNF α) secretion, while acute sleep deprivation causes a raised level of IL-6 on the following day and this pro-inflammatory stimulus could promote plaque instability [375]. One small study from Greece showed a protective effect of an afternoon siesta, which may partly explain the lower rate of AMI seen in Mediterranean countries [376]. Abnormal sleep such as that seen in the sleep apnoea syndrome has also been implicated in the increased morning incidence of AMI [294].

5.7 BEHAVIOURAL TRIGGERS OF ACS

5.7.1 Tobacco Smoking

Smoking is a potent trigger of myocardial ischaemia, which is five times more likely to occur in patients with coronary artery disease when they smoke a cigarette, but is relatively infrequently identified as a trigger for ACS [254 353]. Acutely, tobacco smoking increases catecholamine levels, heart rate and blood pressure [377]. Platelet turnover, aggregability and beta-thromboglobulin levels rise [378]. Smoking causes increases in white cell count, plasma viscosity, fibrinogen, plasminogen activator inhibitor-1 (PAI-1) activity, tissue plasminogen activator (t-PA) antigen and fibrin D-dimer[362]. Smoking increases platelet-thrombus formation and impairs vascular release of t-PA leading to impaired fibrinolytic capacity [379]. Smoking also leads to decreased myocardial perfusion [380] and coronary artery vasoconstriction [381] possibly because of acute impairment of endothelial function[379]. It is associated with increases in levels of CRP, IL-6, TNF-α and the adhesion molecule sICAM in otherwise healthy men[360 361 382]. Cigarette smoking leads to increased superoxide and other reactive oxygen species and decreased levels of anti-oxidants such as ascorbic acid, methionine, cysteine and uric acid [383].

However, despite the extensive evidence that smoking increases the risk of ACS, there is little evidence to date of direct triggering of ACS by tobacco smoking. This is partly due to the nature of cigarette smoking; unless symptoms begin during sleep, a heavy smoker is likely to have smoked tobacco within one or two hours of symptom onset, but this may be no different from periods that do not precede ACS. There have been scarce reports of triggering by tobacco smoking from most of the large scale studies reviewed here. In the series of patients described by Miric et al [310], "nicotine abuse" (defined as smoking at

least twice as much as usual in the previous 24 hours) was associated with inferior rather than anterior infarction, but no comparison condition was included in this analysis.

5.7.3 Cocaine and marijuana

The increased use of cocaine has lead to a rise in the incidence of drug related cardiovascular problems. In 1999 the National Institute on Drug Abuse estimated that 25 million Americans had used cocaine at least once [384], and some 1.5 million to 5 million were current users. Cocaine causes a large, abrupt and transient rise in the risk of MI [313]. Out of 3,946 patients interviewed regarding cocaine in the Onset study, 1% (38 patients) reported cocaine use in the preceding year and 9 patients used cocaine in the hour preceding symptom onset. The risk of AMI was increased 24 times (C.I. 8.5 to 66.3) during the hour after cocaine use[313]. Users were more likely to be male, younger, current cigarette smokers, and ethnic minority group members than were other patients in the study. Many individuals attend emergency departments with cocaine-associated chest pain. In the USA, these individuals are typically young, male, African-Americans with relatively low levels of cardiovascular risk factors. The incidence of acute MI in this population is about 6% [385]. Individuals with cocaine-associated MI tend to have less coronary artery stenosis and less intracoronary thrombus than other acute MI patients [386].

Cocaine has marked sympathomimetic actions, causing elevations in heart rate, blood pressure and myocardial contractility. It has a direct vasoconstrictive effect on the coronary arteries (via an alpha adrenergic effect). This coronary vasoconstriction is more pronounced in diseased than healthy vessels, and is magnified when cocaine use is accompanied by cigarette smoking [387]. Cocaine also enhances platelet activation and

aggregability, and increases PAI-1 levels, the expression of adhesion molecules, and endothelial permeability [384].

The potential of marijuana to trigger ACS was also assessed in the Onset study [314]. Again, the absolute rates of triggering were low, with only 37 of 3882 patients admitting to marijuana use in the 24-hours before cardiac symptoms, and 9 within one hour of symptom onset. The relative risk of symptom onset in the hour after use was 4.8 (C.I. 2.4 to 9.5), with a non-significant increase in risk of 1.7 in the second hour after smoking. 3.2% of the total study population reported smoking marijuana in the preceding year with the proportion being greater in younger patients. Marijuana users were more likely to be younger, male, current cigarette smokers and obese.

5.7.4 Alcohol

There is a well established J-shaped or U-shaped relationship between mortality and alcohol intake in the general population with the lowest level in regular moderate drinkers and this pattern has been established for patients with CAD as well[388 389 390]. Controversy still continues as to whether it is merely the presence of alcohol itself that is beneficial, or whether some beverages such as red wine have a greater protective effect than others [391].

It is possible that heavy drinking is an acute trigger for ACS, but definitive proof is lacking. Prospectively, binge drinking of beer increased risk of death in a sample of middle-aged men in Finland, independently of total alcohol consumption [392]. The relative risk of fatal MI in those who consumed 6 or more bottles (compared with fewer

than 3) was 6.50 (95% confidence interval 2.05 to 20.61), independently of other risk factors.

The acute biological response to alcohol differs with the level of intake. A moderate dose has been shown to reduce measures of platelet aggregation, while large doses inhibit intrinsic fibrinolysis, [393], enhance platelet activation, and are independently associated with higher levels of PAI-1 activity, t-PA antigen, Factor VII , fibrinogen and white blood cell count, effects that persists for several hours [394]. Alcohol raises myocardial oxygen demand via an effect on pulse rate, systolic blood pressure and cardiac output simultaneously, causing a dose-dependent depression in myocardial function [395]. Animal studies have shown that alcohol causes acute dose-related coronary artery vasoconstriction [396].

Clinical studies have produced variable results, although some clear cases of alcohol triggering have been described [397]. McElduff et al [398] reported a protective effect of drinking up to 8 drinks in men and 4 drinks in women on acute MI or cardiac death over the previous 24 hours in people who described themselves as drinkers in a case-control study in Australia. However, the drinkers who abstained from consumption in the previous 24 hours may have been experiencing prodromal symptoms or cardiac problems, so may not be an appropriate comparison group. There was some indication in this study of an increased risk in men and women who drank above these levels, but the number of people in these categories was very small. Also pertinent is a case control study of patients admitted for acute brain infarction [399]. The relative risk for patients who had consumed a large amount of alcohol in the previous 24-hours was 4.19 (C.I. 2.24 to 7.81), while light drinking was not associated with risk. Risk was particularly high in patients who were also hypertensive.

There can be difficulties in the estimation of the true effect of factors such as tobacco smoking, use of marijuana, cocaine or alcohol, as patients may not accurately report actions that they might consider socially unacceptable or that they could feel blamed for. It is also important to note that many behavioural risk factors such as smoking and alcohol consumption may increase in frequency or intensity at times of emotional stress.

5.7.5 Overeating and High Fat Meals

As well as increasing the long-term risk of atherosclerotic coronary artery disease, high fat meals have been hypothesized to have a potential role in the triggering of ACS [400]. Vogel et al found that a fatty meal impairs endothelial function in the four hour post-prandial period, an effect that is independent from changes in total or LDL-cholesterol [401]. However other authors have not replicated these findings[402]. Post-prandial lipoproteinaemia may also have an effect on increased oxidative stress, hypercoagulability, resistance to fibrinolysis and platelet activation [400].

The evidence that high fat meals or excessive food intake trigger ACS is modest. Overeating in the period preceding symptom onset was reported by a small proportion of patients in the MILIS study [254], but in the absence of control data it is not possible to determine whether this was an unusual or common event in the patients' lives. No data concerning triggering by overeating has been reported from other large scale studies.

5.8 EMOTIONAL STRESS AS A TRIGGER OF ACS

5.8.1 Earthquakes

One way of assessing the effects of acute stress on a population is to examine the patterns of hospital admissions and cardiac deaths after emotionally charged events such as natural disasters, conflicts and even major sporting events. A number of studies have examined the rates of cardiovascular events associated with experiencing an earthquake. Natural disasters of this type lead to widespread devastation, with long-term as well as acute effects on cardiac health [403] [404]. In studies of acute effects, it is important to distinguish between cardiac events resulting from the severe stress of living through an earthquake, from those due to sudden physical exercise (e.g. running away from buildings), or direct injury and trauma. The impact of several earthquakes on cardiovascular events have been published over recent years [405-408] [409], and effects have not been consistent [410] [411], although the majority of studies have shown an increase in cardiovascular death and ACS admissions in the days, weeks, and months after the earthquake compared with the antecedent time.

The most thorough analyses have been those carried out following the Northridge Earthquake in the Los Angeles area in January 1994 [410-412]. A postal survey of more than 100 hospitals in the area showed that the number of admissions for acute MI increased from 149 in the week before to 201 in the week after the earthquake [411]. Examination of the coroners records for Los Angeles County revealed that the number of sudden deaths from cardiac causes increased from an average of 4.6 per day in the preceding week to 24 on the day of the earthquake [412]. Only three of these cases were associated with unusual physical exertion, and the vast majority (92%) had cardiovascular risk factors,

though not necessarily a clinical history of disease. A further analysis examined all deaths in the county, and confirmed the increase in deaths from CAD on the day of the earthquake[410]. There was no increase in deaths from other cardiovascular diseases such as cardiomyopathy or from noncardiovascular causes, suggesting a specific association with coronary artery disease. Interestingly, the population design of this study allowed the issue of whether cardiac events were brought forward in time to be analyzed. Deaths from CAD and SCD were less frequent than average in the first or second week after the earthquake, suggesting that the acutely traumatic event had caused fatal cardiac events in people who were highly vulnerable to ACS [410 412].

Analyses of the Hanshin-Awaji earthquake in 1995 in Japan are consistent with these findings, with a substantial increase in the number of patients admitted with acute MI on the day of the event [413]. However, in this case, the increase in fatal MI persisted for up to 8 weeks following the earthquake [406]. This effect varied by regions around the prefecture, with greater mortality in areas where there was greater material damage, suggesting that the ongoing mental and financial strain of trying to restore everyday life may have contributed. Somewhat smaller increases in rates were recorded following earthquakes in Greece and Australia[407 408].

One exception to this association between earthquakes and triggering was seen in the period following the 1989 Loma Prieta earthquake in the San Francisco Bay area. There was no statistically significant increase in AMI admissions in the San Francisco Bay Area on the day of the Loma Prieta earthquake compared with the days before or after the earthquake or compared with the same day in 1990. In contrast, there was a 110% increase in admission rate for AMI in Los Angeles County on the day of the Northridge earthquake compared with the average of the 7 days before the earthquake ($z = 4.349$, P

<.001). A possible explanation may lie in the timing of this event. Brown [405] compared the cardiac consequences of the Loma Prieta and Northridge earthquakes, and noted that the Northridge earthquake struck at 4.31 am whereas the Loma Prieta earthquake (an event of similar magnitude) struck at 17.04 pm. This suggests that risk is greater during the vulnerable morning period. The Northridge earthquake occurred on a Monday in January, while the Loma Prieta earthquake occurred on a Tuesday in October. There is a greater susceptibility to acute MI in winter months, and from other information about timing of infarctions, a Monday morning in the winter is among the most lethal times for an event such as this to take place [319]. The Northridge earthquake thus had its effect on AMI and death from a particularly lethal combination of timing (hour, day and season) and triggering. The Hanshin-Awaji earthquake also struck early on a Tuesday morning on a winter's day in the Kobe area of Japan.

Not surprisingly, there have been few direct studies of acute changes in the pathophysiological mechanisms that might underlie triggering by earthquakes. Presumably, the processes resemble those involved in triggering by emotional stress and negative emotions, detailed later in this review. Fortuitously, however, a research group in Taiwan were carrying out Holter monitoring on 15 patients with suspected coronary artery disease when the island was struck by a major earthquake in 1999[414]. Spectral analysis documented a marked increase in low frequency to high frequency ratio for about 40 minutes after the earthquake, indicative of vagal withdrawal. ST-segment depression occurred in several patients, and was correlated with the increase in low frequency power. Parati et al [415] have described a single patient who was undergoing ambulatory blood pressure monitoring during a moderate severity earthquake in central Italy. There was a marked increase in systolic and diastolic pressure and in heart rate which persisted for an hour, and the next 6 hours were characterised by high blood

pressure variability. Less acute effects that have been reported include increased blood viscosity, fibrinogen and D-dimer levels[416](102), an increase in deep negative T waves without Q waves, and abnormal cardiac sympathetic function as revealed with metaiodobenzyl guanidine imaging [417].

Blood pressure has been seen to be raised for several weeks after an earthquake as well as blood viscosity with abnormities persisting for up to six months after the earthquake, but there are no data on myocardial ischaemia [417 a-c]. This prolonged effect may have potential importance in the sphere of litigation regarding cardiac events occurring in the aftermath of stressful circumstances.

5.8.2 Sporting events

The quarter-final of the 1996 European football championships between the French and Dutch sides resulted in a draw at the end of extra time and so went to a penalty shoot out which the French won. The impact of this exciting event was studied in an analysis of mortality in the complete population of Dutch men and women aged 45 or more. There was a relative risk of death from AMI or stroke of 1.51 (95% confidence interval 1.08 to 2.09) for men on the day of the match, compared with the five days on either side, with no effect on women [418]. No such effect was seen among French men [419]. A pattern of increased hospital admissions was seen for AMI in England on the day of the country's 1998 World Cup match with Argentina,[420]. This match again ended in a penalty shoot out and England lost. There was a 25% increase in hospital admissions for both men and women and no concurrent rise in admissions due to causes such as accident or trauma, making it less likely that alcohol played a significant part in triggering. Other studies have failed to observe any increase in ACS on the days of international matches, possibly

because these did not involve penalty shoot outs which are an especially tense way to conclude the game[420 421]. Regrettably the recent penalty shoot out between England and Portugal in the 2004 European football Championships was also associated with reports of AMI and cardiac death in the period immediately afterwards [422].

On the other hand, a more recent study of football matches played by teams from the North-East of England over a 5 year period demonstrated a modest increase in deaths attributable to acute MI and stroke in men (but not women) on the days on which these teams lost [423]. For example on days when Sunderland AFC lost at home there was a 1.63 (95% CI 1.16 – 2.3) relative risk of male death from AMI or stroke. The circumstances surrounding these deaths are not known, so it is possible that physical exertion, emotional stress, and alcohol consumption all contributed to triggering. Conversely Berthier et al found that there was a decrease in AMI mortality when France won the 1998 football world cup [424] – so perhaps it is not just the taking part but the winning that is important as well!

5.8.3 War

In the initial phases of the Gulf War in 1991, the incidence of acute myocardial infarction increased in an area near Tel Aviv, which was close to but not directly affected by missile attacks [425]. Although negative results from other centres have been published [426], this finding from a single hospital was subsequently confirmed in a national survey in Israel, in which there was a 58% increase in total mortality on the day of the first missile strikes [427]that was largely attributable to AMI and SCD. There was no excess mortality over the following 16 days, suggesting either that susceptible individuals had succumbed, or that the population adapted to the stress. A rise in the incidence of ACS (especially Q-wave AMI) and in the mortality from AMI was also reported in Zagreb,

Croatia in 1991 at a time of air-raid alarms [428]. Chi et al [429 430] have examined cardiac death rates and admissions to acute coronary care in New York City in the period surrounding September 11th 2001. No excess rates were observed. Feng et al however recently presented data from Brooklyn, New York showing an increase in proportion of hospital admissions with AMI (by 35%) in the 60 days after the September 11th attacks with an interesting coincidental 17% decrease in the proportion of patients admitted with a diagnosis of UA, suggesting that the additional mental stress of the time modified some of the patients who would have otherwise presented with UA into AMI [431].

5.8.4 Other External Events

An intriguing illustration of the possible triggering effect of psychological stress was seen in a study of Chinese and Japanese people in the United States [432]. The number four is a traditionally unlucky number, and evokes discomfort in some Chinese and Japanese people. For example, some buildings in China or Japan do not have a fourth floor as this is felt to be unlucky. A study of the death certificates of more than 47 million Americans between 1973 and 1998 showed a peak in cardiac mortality in people of Chinese or Japanese origin on the "unlucky" fourth of the month compared with any other day of the month. This was not seen in white Americans or in Chinese and Japanese Americans dying from non-cardiac causes suggesting a role for psychological stress as a precipitant.

5.8.5 Emotional Upset

As noted earlier, emotional upset is among the most commonly reported triggers of ACS. However, such reports may be particularly susceptible to premonitory symptoms and to retrospective reporting bias, so careful analysis and appropriate statistical analysis is

required. The TRIMM study was primarily concerned with physical exertion as a trigger, but also assessed emotional factors [346]. Emotional upset was reported by 4.4% of patients in the 24 hours prior to onset, with a relative risk in the case-control analysis of 2.7 (C.I. 1.1 to 6.6). There was a suggestion that events such as death of a friend or family member or unusual dreams or nightmares, were also linked to increased risk, but the number of such occurrences was small. The association with emotional upset and stress at work in the four weeks prior to acute MI was also significant (odds ratio of 2.5). In another study, patients admitted with AMI report a greater incidence of high levels of subjective mental stress in the 4 weeks prior to admission compared with controls (53% versus 20% $p < 0.005$)[433]. In a post MI population antecedent stress carries a 2.5 times greater risk of reinfarction compared with controls [434].

Depression may act as an inflammatory stimulus to atherosclerosis chronically but there is little data to support it as an acute trigger factor [282]. There may be a sex difference in the reporting of stress as an acute trigger, Culic et al [318] reported that stress was mentioned by twice as many female than male patients. In the Onset study, participants completed the anxiety subscale from the State-Trait Personality Inventory for the 2 hours prior to acute MI, and for a control period 24 hours earlier [115]. The relative risk of having a score above the 75th percentile during the 2 hour hazard period was 1.6 (C.I. 1.1 to 2.2).

5.8.6 Anger

The role of anger as a possible trigger of ACS has been assessed in two studies. An analysis of the Onset study indicated that 39 out of 1623 patients reported being very angry or furious in the 2 hours prior to acute MI, an incidence of 2.4% [115]. In comparison with usual levels of anger, the relative risk of acute MI in the two hours after

an episode of anger was 2.3 (C.I. 1.7 to 3.2), and in comparison with a control period 24 hours earlier it was 4.0 (C.I. 1.9 to 9.4). This effect was independent of age, sex, cardiovascular risk factors, and the use of beta-blockers. The association between anger and symptom onset was confirmed in the SHEEP study, in which the absolute incidence of intense anger in the hour preceding onset was 1.2% [316]. The relative risk (compared with usual levels of anger) was 9.0 (C.I. 4.4 to 18.2), but increased to 15.7 (C.I. 7.6 to 32.4) when analysis was limited to patients who had no premonitory symptoms.

These studies have also explored other factors that might influence the likelihood of anger being a trigger. In the Onset study, aspirin had a protective effect, suggesting a key role for platelets in the pathophysiology of anger induced AMI. In the SHEEP study anger triggering was more common among individuals who reported very infrequent anger under normal conditions suggesting that angry individuals may become accustomed to the physiological effects of anger. Most interestingly, the risk of anger triggering was inversely related to socioeconomic status as indexed by educational attainment in the Onset study [312]. The relative risk varied from 3.3 (C.I. 2.0 to 5.4) in patients with less than high school attainment, to 1.6 (C.I. 0.9 to 2.9) in those with college education. This result is potentially important in the light of the known association between low socioeconomic status and CAD and suggests that socioeconomic factors may act as modulators of acute psychological triggers. This may be related to differences in psychobiological reactivity associated with socioeconomic position [435]. In healthy middle-aged men and women, mental stress elicits more prolonged increases in prothrombotic variables (Factor VIII, plasma viscosity and whole blood viscosity) in lower compared with higher socioeconomic groups [178]. Anger and hostility have both been shown to increase stress-induced platelet activation [174 436]. Anger, hostility and depression have also been related to plasma IL-6 levels[437]. Anger is

a particularly potent inducer of transient myocardial ischaemia in patients with coronary artery disease both in the laboratory [438] and in daily life [353].

5.9 EMOTIONAL STRESS AND SUDDEN CARDIAC DEATH

The vast majority of patients with SCD have either intracoronary thrombus or evidence of plaque fissuring as compared with controls [16]. It may be assumed that the majority of cases of SCD are due to atherosclerotic plaque rupture and so are subject to the triggering influences discussed above.

There have been few studies of possible emotional triggers of SCD over recent years, though earlier work suggested a connection [439 440]. One of the most thorough studies was carried out with the relatives of 100 men aged 70 years or less who died suddenly, and who were interviewed within 10 days about the circumstances surrounding the death. Results were compared with those collected from 100 MI admissions [441]. Coronary risk profiles did not differ, but the men who suffered a sudden death were more likely to have consumed alcohol within 3 hours of symptoms. They were also significantly more likely to have experienced moderate or severe stress in the 30 minutes prior to onset (23% versus 8%). Although the study involved a selected sample of cases meriting necropsy by the coroner's office, and neither the informants nor investigators were blind to group, the results are consistent with emotional stress being a trigger in many cases of SCD as well as nonfatal ACS.

There are a number of cases of SCD in which coronary artery pathology is not the cause. The majority of these deaths are probably arrhythmic, with coronary artery spasm

playing a role in a small number. These cases usually have a structural abnormality of the myocardium (hypertrophic cardiomyopathy, ventricular hypertrophy, previous ischaemic damage) which acts as an arrhythmogenic substrate. There is extensive documentation in the literature of emotional stress leading to sudden cardiac death and evidence linking stress with dysrhythmia [442]. One of the main culprits identified is an imbalance in the autonomic nervous system leading to a sympathetic dominance, and the massive sympathetic discharge associated with anger, grief, or acute emotional upset might be a potent arrhythmic stimulus [443]. There is also evidence to support decreased heart rate variability with increased sympathetic and decreased parasympathetic influence [444]. The sympathetic overactivity related to stress may also play a part in determining the susceptibility of the ischaemic myocardium to arrhythmia during ACS. The advent of the implantable defibrillator has provided a valuable tool for examining ventricular tachycardia and fibrillation. Psychological stress, and in particular the experience of anger, has been shown to trigger dysrhythmia, leading to activation of the defibrillator [445]. Recently there was an increase found in defibrillator discharges in patients living in Florida in the 30 days after the September 11th attack on the World Trade Centre compared with a control period suggesting an influence of psychological stress [446]. A second similar study has found that there was an increase in ventricular arrhythmias for the 30 day period after September 11th 2001 suggesting a role for ongoing sub-acute stress in arrhythmogenesis [447].

5.10. PATHOPYSIOLOGICAL MECHANISMS UNDERLYING THE EFFECTS OF EMOTIONAL STRESS

There are several mechanisms through which acute emotional stress might trigger ACS in vulnerable individuals. One of the main culprits is likely to the sympathetic activation

and increase in circulating catecholamines which are a response to stressful stimuli. Amongst other things these may have an effect on haemodynamics, vascular tone and platelet activation.

Inflammatory cytokines production is associated with psychological stress. For instance, academic stress has been shown to stimulate production of IL-6, TNF-α and interleukin 1 receptor antagonist (IL-1Ra) in students who experience high levels of distress [166]. The chronic stress of looking after a dementing relative is associated with increased IL-6 concentration [167]. Increases in the plasma concentration of IL-6 and TNF-α have been reported in the 45-minutes to two hours following standardised mental stress in the laboratory [448]. These responses are correlated with the magnitude of cardiovascular reactions [161] suggesting that inflammatory cytokine responses are associated with sympathetic nervous system reactivity. The increase in plasma IL-6 over 2 hours post-stress is also greater in people of lower socioeconomic status [449].

Acute mental stress induces alterations in the expression of adhesion molecules such as L-selectin as well as members of the integrin family of molecules [450], a finding which was more pronounced in younger participants. Such alterations in adhesion molecule expression may contribute towards changes in plaque stability and progression of atherosclerosis. In addition, mental stress increases the chemotactic responses of peripheral blood mononuclear cells and increases the numbers of immunoregulatory cells via adrenergic receptor antagonism [451 452]. There is redistribution of white cells from the blood to the tissues and sites of inflammation. These cells are crucial to the process of atherosclerosis and so alterations in their number and function might be critical.

Even short stressful tasks induce transient endothelial dysfunction assessed using flow mediated dilatation that may continue at least 90 minutes after termination of the challenge[154] [453]. A recent study of junior physicians documented impairment of endothelial dysfunction following long work shifts [454].

The haematological response to stress in healthy individuals involves an activation of the coagulation and fibrinolytic pathways simultaneously. It has been suggested that in patients with coronary artery disease, the procoagulant changes outweigh the anticoagulant effects because of impairment of vascular endothelial function [455]. Acute mental stress also causes an increase in the concentration of platelet activating factors such as thrombin [456], platelet factor 4, beta-thromboglobulin and catecholamines as well as increase in blood haematocrit and viscosity [457]. Mental stress is associated with increases in the number of platelet aggregates and overall aggregability (with ADP or collagen) in comparisons of post myocardial infarction patients and healthy controls [359] [458]. Although there is currently little data on the potential role of depression or depressive symptoms as catalysts for ACS, one potential mechanism by which they could be involved is that depressed persons display an exaggerated serotonin-mediated platelet reactivity [171]. This could partly explain the trend towards benefit seen in the SADHART study [207] (see Chapter 3).

Mental stress is also a potent cause of myocardial ischaemia [438] and is able to cause reversible endothelial dysfunction via endothelin-A receptors [459]. Naturalistic studies of patients with coronary artery disease using Holter monitoring indicate that mental stress in everyday life is frequently associated with transient silent myocardial ischaemia. Gabbay et al monitored 63 patients with coronary artery disease, having them complete a comprehensive diary of activities and moods[353]. When patients reported high levels of

anxiety or anger, ischemia was present for 5% of the time, compared with lower levels when mental activity was more moderate, and only 0.2% of the time when patients were resting or sleeping. Using a case-crossover analysis, Gullette et al [354] reported a relative risk of 2.2 (C.I. 1.1 to 5.4) for myocardial ischemia following high compared with low levels of tension, after adjusting for physical activity and time of day. The relative risk for depression was also 2.2, but with wider confidence intervals.

Anger is a particularly potent inducer of transient myocardial ischaemia in patients with coronary artery disease both in the laboratory [438] and in daily life [353]. Anger elicits pronounced haemodynamic responses, and can lead to coronary vasoconstriction in vulnerable individuals [438]. Anger is also a precipitant of ventricular dysrhythmia. In a study of patients with implanted cardioverter-defibrillators, anger rated as moderate or greater by patients led to an increased incidence of shocks received compared with control periods [347].

Autonomic balance and cardiac arrhythmia are also sensitive to acute emotional stress [443]. One of the main culprits identified is an imbalance in autonomic control leading to sympathetic dominance that is associated with vulnerability of ventricular arrhythmias. Kop et al [460] performed power spectrum analysis of ambulatory ECG signals during periods of stress-induced myocardial ischemia in patients with stable coronary artery disease. They found that when ischemic events took place during periods of higher mental activity (including anger and anxiety); the ischemia was preceded by parasympathetic withdrawal, and sympathetic dominance over cardiac rhythm.

5.11. METHODOLOGICAL ISSUES IN STUDYING TRIGGERS

The use of case-control and case-crossover designs has greatly increased the confidence with which conclusions can be drawn about emotional and behavioural triggers, since these methods overcome many of the biases present in studying acute causes. Nevertheless, a cautious attitude to interpretation is necessary because of several factors in the design of these studies.

5.11.1 Retrospective reporting bias

Neither the case-crossover nor case control designs can eliminate biases in reporting. Even though the same patients provide information for hazard and control periods in the case-crossover design, individuals with ACS may emphasize emotional or other triggers in the pre-symptomatic period, as they develop their cognitive representation of the cardiac event[320]. One method of helping to address this issue would be to seek verification of the patient's behaviour or emotional state from bystanders or relatives who witnessed the circumstances. This has not been done in the major studies of triggers, and data have derived almost completely from patients themselves.

5.11.2 Memory decay and salience

In the case-crossover design, the control period is more distant in time than the hazard period [321], and may lack the salience of the hours preceding symptom onset. Memory for these control periods may not therefore be as accurate as for the hazard period. Additionally, a common control period selected in these designs is the usual level of exposure in the week, 6 months or year preceding ACS onset. This requires patients to estimate how often they were usually angry, physically active, taking cocaine, etc., over an extended period of time. Behavioural estimates are typically much less accurate for

extended time periods than for specific intervals that can be accessed in memory through prompts or cues. It may be, therefore, that the relative risks for hazard periods compared with usual levels are less reliable in these analyses than in comparisons with specific defined periods of the same length (such as the same one or two hours on the preceding day). Recent work has examined two types of differential misclassification of exposure in case-crossover studies. The exposures were outcome-dependent misclassification of exposure (if an event has occurred than it could affect reporting of exposure) and differential misclassification of exposure as a result of memory fading over time. Study was done in a population with Menière's disease looking at the exposures of mental stress an salty food intake and found that neither differential misclassification of exposure caused a significant difference in accuracy of exposure reporting[461].

5.11.3 Premonitory and prodromal symptoms

A particularly important issue is whether the trigger events precede acute symptoms, or whether there were premonitory signs or silent prodromal events. Trigger studies have varied in whether they included or excluded cases with premonitory symptoms. The presence of premonitory symptoms may alter the hypothesized causal chain, and reverse causation may operate. For example, there are large and rapid increases in inflammatory markers such as IL-6 and C-reactive protein at the early stages of ACS [462] [463]. Inflammatory stimuli have been shown to induce acute negative emotional states, even when the stimulus is relatively mild [464] [465]. Hence, it is conceivable some "triggers" are actually consequences of early manifestations of plaque disruption.

5.11.4 Presentation bias

A proportion of acute cardiac events do not lead to hospitalization, but either to preadmission death or to myocardial damage that is clinically undetected and only comes to light at a later stage, if at all [466 467]. It is well established that psychological, social and contextual factors influence the presentation of bodily complaints [468]. It is conceivable, therefore, that triggers do not have a direct effect on the occurrence of ACS, but rather influence symptom reporting and health-seeking behaviour. Perhaps individuals with ACS in the absence of triggering phenomena are less likely to attend emergency departments or contact their physicians, leading to a preponderance of trigger cases in interview studies. This factor is difficult to discount in the absence of population-based survey methods.

5.11.5 Direct measures of underlying pathology

To date, no studies of triggering of ACS have combined measures of emotional and behavioural factors with direct assessments of plaque activity. New imaging techniques such as intravascular ultrasound scanning and thermography are providing *in vivo* information about plaque rupture and erosion, and integrating such methods into triggering studies would be very informative although very difficult. It would allow the assessment of whether triggering is associated with the rupture of highly vulnerable plaques, with alterations in haemodynamics, or with a prothrombotic haemostatic profile, thus permitting the alternative pathological sequences outlined earlier in this review to be distinguished.

5.12 CONCLUSIONS

There is a growing body of evidence to support the role of behavioural and emotional triggers in ACS. It is likely that triggers are more potent when acting in combination, or

when they are present at particular times of day. The evidence of triggering by physical exertion and emotional stress is compelling. Findings related to sexual activity, the use of cocaine and marijuana are consistent, but have not yet been documented in many cohorts. There is good reason to suspect that heavy drinking can be a trigger, but proof is lacking. Some factors that might be relevant have not been evaluated so far, such as acute depression. There is growing evidence that factors identified as triggers have appropriate effects on endothelial function, inflammatory responses, haemostasis and platelet function, and on autonomic cardiac control. However, no studies have yet integrated this pathophysiological perspective into clinical investigations of triggering of ACS. It is possible that different mechanisms are involved in the action of different types of trigger; some may act primarily through haemodynamic effects causing increased shear stress across the atherosclerotic plaque, others may render the plaque more vulnerable through inflammation, or increase the likelihood that plaque disruption will be associated with thrombus formation. Experimental studies involving assessments of haemostatic and inflammatory responses to potential triggers in patients who have survived ACS may further clarify the pathophysiological mechanisms underlying the triggering process. Methodology has progressed considerably over recent years, but there remain limitations to study designs that influence the conclusions that can be drawn. Nevertheless, the study of triggers of ACS is in an exciting phase, with the possibility that information from different types of investigation can be brought together to promote methods of identifying individuals at risk, so that specific interventions designed to prevent ACS can be instituted.

Chapter Six

MENTAL STRESS INDUCED MYOCARDIAL ISCHAEMIA – A SYSTEMATIC REVIEW

6.1 INTRODUCTION

An important method of assessing the effects of acute mental stress on cardiac function is by measuring transient ischaemic responses to standardised mental stress tests. Mental stress-induced myocardial ischaemia (MSIMI) is analogous to exercise stress ischaemia, except that the stimulus is psychological rather than physical. Although the mechanisms of plaque rupture and MSIMI are likely to have some pathophysiological differences, some of the underlying mechanism may be common to both entities, and the occurrence of MSIMI may well be an important precursor in some cases of SCD. MSIMI has been studied with a number of different imaging techniques and with a range of stressful stimuli. But several investigations have involved small numbers of patients, and the medication status of patients has been variable. This has resulted in diverse findings concerning the prevalence of MSIMI, the conditions in which it is elicited, the type of patients who are most susceptible, the potential mechanisms underlying the phenomenon, and its clinical significance. In an effort to clarify these issues, the studies in which myocardial ischaemic responses have been measured in response to standardised mental stressors in the laboratory and clinic have been systematically reviewed. A shorter version of this review was published in 2003 [438]

6.2 METHODS

Relevant articles were identified from searches of PubMed (www.ncbi.nlm.nih.gov /PubMed) between 1980 and 2002 by Professor Steptoe and myself individually. Only articles in English language peer-reviewed publications were examined. Internet searching was done solely with the Pubmed database as this contains the overwhelming majority of peer-reviewed publications in this area. Studies were assessed that examined the link between standardised mental stress tests and myocardial ischaemic responses. The search terms used were (mental OR psychologic OR psychological) AND stress AND (cardiac OR myocardial OR myocardium) AND (ischaemia OR ischaemic OR ischemia OR ischemic). This search yielded 783 responses that were assessed for original articles with laboratory assessment of ischaemia. Studies involving both patients with CAD and healthy volunteers or patients without CAD were included. To ensure comprehensive data location, further searches were made for authors published in this field and review articles were used as sources. The bibliographies of all papers retrieved were hand searched to ensure as many articles as possible were obtained. A number of studies in this field have resulted in multiple publications, addressing different aspects of MSIMI. Only the primary publication has been included in this main review, but subsequent publications were scrutinised when addressing ancillary issues. A wide range of stimuli were regarded as mental stressors, including mental arithmetic, simulated public speaking tasks, problem solving tasks, cognitive tasks like the Stroop colour/word interference task, psychomotor challenges such as mirror tracing, and tasks involving the recall of negative emotion. Responses to the cold pressor test (immersion of hand or foot in iced water) and hyperventilation tasks were excluded since these elicit reflex physiological responses that are not psychological in origin [469]. Studies have been categorised according to the method used for assessment of myocardial ischaemia.

6.3 INCIDENCE OF MENTAL STRESS INDUCED MYOCARDIAL ISCHAEMIA

Methods of assessing myocardial ischaemia vary in cost, ease of administration, exposure of patients to radiation, sensitivity and test-retest reliability. Investigations that assessed transient MSIMI using the electrocardiogram (ECG) alone, echocardiography, the radionuclide ventriculogram, stationary or ambulatory nuclear probes, positron emission tomography (PET), and quantitative coronary angiography were separately reviewed.

A number of general points emerge from this review, regardless of the stressors used or method of ischaemia assessment. Firstly, MSIMI is much more common among patients with CAD than other groups, although significant numbers of individuals without known CAD also show ischaemic responses according to some criteria. MSIMI is largely a silent phenomenon, and anginal chest pain is rare [470-474]. Thirdly, the vast majority of CAD patients who experience MSIMI also demonstrate exercise-induced ischaemia [472 475 476]. The proportion of patients who test positive for mental stress but negative for exercise-induced ischaemia is relatively low. Fourthly, the rates of MSIMI are highly variable across studies, even with the same method of assessing ischaemia and with similar mental stress tests. Finally, most studies to date have been carried out with men, and the extent of effects on mental stress in women is not known.

6.3.1 Studies involving ECG assessment

The studies with just ECG assessment of mental stress testing were the first studies to be performed. The ECG is simple, cheap, non-invasive and reproducible. As has been

subsequently been shown, the ECG is a relatively insensitive tool for the detection of mental stress ischaemia. The ECG is however more sensitive than symptomatic angina during mental stress testing.

Eight studies have used ST segment depression as the primary method for assessing myocardial ischaemia, although other investigators have included the ECG along with more sophisticated imaging techniques. Mental arithmetic has been the commonest mental stressor, but general knowledge quizzes, reaction time tasks, simulated speech tasks, and the Stroop test have also been employed. The incidence of MSIMI in patients with CAD averaged 30% using ECG criteria, with a range across studies of 12 – 55% (table 6.1). The lowest incidence was observed in a study in which patients were medicated with beta-blockers and calcium antagonists [477], while in other studies patients were withdrawn from medication. A study of patients with vasospastic angina and no significant CAD showed an incidence of 28% [478]. In a large cohort of the siblings of patients with premature CAD, none of the participants displayed MSIMI [479]. Two other studies included individuals without CAD. No MSIMI was observed by Jennings *et al* [480] in a non-CAD control group, while Specchia *et al* [481] reported that 18% of patients with chest pain but without significant stenosis on angiography fulfilled ECG criteria for MSIMI. It is possible that some of these individuals had vasospastic angina.

Interestingly, studies that have assessed ECG secondarily to cardiac imaging have reported rather lower rates of ST-segment depression than those shown in Table 6.1. For example, in the Psychophysiological Investigations of Myocardial Ischemia (PIMI) study, 58% of cardiac patients displayed MSIMI as defined by worsening wall motion abnormalities and/or left ventricular ejection fraction reductions ≥8%, but the incidence of ECG-defined ischaemia was only 2-3%[482]. Andrews *et al* found that 53% of patients

exhibited new wall motion abnormalities during mental stress, but only 7% showed ST-segment depression[483]. The explanation for this discrepancy is not clear.

6.3.2 Studies using radionuclide ventriculography

Studies using radionuclide ventriculography are the most numerous in the literature. Radionuclide ventriculography is safe, non-invasive, widely available, and reproducible, and can be applied to both exercise and mental stress testing. The method can be used for serial imaging, and also has the benefit of identifying dysfunctions in arterial territories that can be related to abnormalities on catheterisation or perfusion imaging.

Three criteria for MSIMI have been used (Table 6.2): the presence of new or worsening wall motion abnormalities, a fall in ejection fraction of ≥ 5 %, and a fall in ejection fraction of $\geq 8\%$. Overall, the incidence of MSIMI using exclusively wall motion abnormality criteria averaged 46% in patients with CAD, while incidence on the ejection fraction criteria selected by the investigators averaged 29%. However, in some studies ejection fraction criteria have proved more sensitive to mental stress [484]. The large PIMI study reported an incidence of 58% using combined criteria [482]. Aggregating across studies and using the most sensitive index in each case, an overall incidence of MSIMI of 48% in CAD patients, ranging from 34% [485] to 74% [476] can be obtained. By contrast, across studies, 20.6% of volunteers or patients without known CAD displayed MSIMI. This is a sizeable proportion, but may be due in part to the use of the criterion of a decrease in ejection fraction of $\geq 5\%$. Becker *et al* [486]showed that 41% of a sample of healthy middle-aged men and women with low coronary risk factors showed MSIMI with the $\geq 5\%$ criterion, but that only 10% displayed wall motion abnormalities, and 17% exhibited reductions of ejection fraction $\geq 8\%$. Consequently a fall in ejection fraction of

$\geq 5\%$ in response to mental stress may not be a sufficiently stringent criterion of myocardial ischaemia in the absence of wall motion abnormalities.

6.3.3 Radionuclide studies involving assessment of perfusion

The majority of radionuclide isotope studies have used radionuclide ventriculography to examine alterations in left ventricular ejection fraction or changes in wall motion. Only three independent studies have used radionuclide perfusion imaging to correlate these criteria of myocardial ischaemia with the effects of mental stress on myocardial perfusion. In people without CAD, quantitative analysis has suggested that mental stress induces a global increase in tracer uptake by the myocardium with no reversible perfusion defects [487].

The three studies assessing myocardial perfusion with scintigraphy have all shown that high rates of new reversible perfusion abnormalities with mental stress (Table 6.3). Two Italian studies of post-infarction patients observed perfusion abnormalities in 70% and 89% cases respectively [488] [489]. All the patients in a study by Kuroda *et al* [490] had reversible perfusion abnormalities. However, the participants in this study had relatively severe CAD, with a mean number of 2.2 diseased vessels in the study group. Only 50% of these patients had a fall in left ventricular ejection fraction $\geq 5\%$, suggesting that perfusion imaging is a more sensitive indicator of MSIMI than is a decrease in ejection fraction.

6.3.4 Studies using echocardiography

There are just a small number of echocardiographic studies in the literature, only two of which have involved more than 20 patients. The mean incidence of MSIMI across studies was 37% in patients with CAD, and 2% in controls (Table 6.4). However, the incidence of MSIMI between studies has ranged from 0% to 61%, despite the same stimulus (mental arithmetic) being used throughout. One study showed that the incidence of MSIMI was positively associated with the number of diseased arteries [473] while a second did not [470].

6.3.5 Studies using the nuclear VEST

The VEST system provides a continuous beat-by-beat measure of left ventricular volumes and ejection fraction, using a radionuclide detector mounted in a vest-like garment. The technique has been validated against conventional blood pool imaging [491] [492]. Studies using the VEST system have all employed an ejection fraction decrease of $\geq$5% to indicate an abnormal cardiac response to mental stress, and consequently the same caveats exist as for radionuclide studies. The range of ischaemic responses varied across studies from 37% to 62% in patients with CAD, with an average of 41% (Table 6.5). In controls without known CAD, the incidence of MSIMI averaged 16%. One study with a sample selected for their predisposition to MSIMI showed highly reproducible ejection fraction responses over a 4-8 week period[493].

6.3.6 Studies involving positron emission tomography (PET)

PET scanning is useful in assessing the effects of mental stress on the heart because it provides measures of coronary artery blood flow and myocardial perfusion. It has not generally been used to define MSIMI, but rather to assess mechanisms (Table 6.6). In volunteers without known CAD, resting blood flow is similar in the three arterial territories, and mental stress causes an increase in myocardial blood flow of some 30%[494]. The increase in myocardial blood flow is correlated with increases in catecholamine levels and rate-pressure product, and there is a decrease in coronary resistance. In contrast, Schoder *et al* [495]reported that in patients with CAD, there was a smaller rise in myocardial blood flow during mental stress, with no increase at all in regions with fixed perfusion defects. One quantitative result has been reported using PET scanning. Deanfield *et al* [474] showed that 75% of patients and no controls had MSIMI as defined by reversible abnormal regional myocardial perfusion. In this study, 38% of patients also fulfilled ECG criteria for MSIMI.

6.4 SUMMARY OF TRIAL DATA

Summarising across the 34 studies that provided quantitative information in this chapter, mental stress induces transient myocardial ischaemia in about 30% of CAD patients using electrocardiographic criteria, and 37-41% of patients with CAD with criteria based on decreased ejection fraction or wall motion abnormalities, while more than 75% of patients have perfusion abnormalities measurable by scintigraphy or PET scanning. Rates of MSIMI in patients without CAD or in healthy volunteers are in the range of 16% (VEST studies) to 21% (radionuclide ventriculography). These figures give only an

approximate estimate of the incidence of transient MSIMI, since the studies differed markedly in size.

Differences in the sensitivity of the method of assessing myocardial function is responsible for some of the variation in rates of MSIMI. But the variability between studies using the same assessment technique is a result of other factors, including the following:

1. The selection of patients. The patients studied have varied substantially in the severity of CAD, cardiac history, age, and other selection criteria. Some studies have only include patients who had positive exercise stress tests [482], and this might have increased the likelihood of observing MSIMI.
2. Nature of stressors. Some mental stress tests are more potent than others in stimulating myocardial ischaemia. Radionuclide studies indicate that public speaking is more potent than mental arithmetic and the Stroop colour/word interference task in eliciting myocardial ischaemia in CAD[472 496 497]. Blumenthal *et al* [485]found that a mirror tracing task was comparable with public speaking in terms of eliciting ischaemia, and that both were superior to mental arithmetic. A study specifically designed to assess reproducibility of responses over time showed that anger recall was a more consistent stimulus for MSIMI than mental arithmetic or the Stroop test[493]. Reaction time tasks appear to be relatively ineffective inducers of myocardial ischaemia [8, 15].
3. Criteria of definition of ischaemia. As discussed previously, the incidence of MSIMI depends upon the diagnostic criteria used. This is particularly relevant in the radionuclide ventriculography studies

   It should be noted that there are no standard agreed protocols for mental stress testing. It cannot be assumed that mental arithmetic, for example, is the same

challenge in different studies. Few studies have collected subjective ratings, behavioural performance measures, or other indicators of stressfulness.

4. Medication status. The use of cardiac medication has varied substantially across studies, and may have contributed to the range of results. Few direct comparisons have been reported. One double-blind study found that a limited effect of metoprolol, reducing the incidence of MSIMI (defined by worsening wall motion abnormality) from 74% to 64% [476]. By contrast, Andrew *et al* [483] reported that wall motion abnormalities during mental stress were prevented by nifedipine or atenolol.

6.5 MECHANISMS UNDERLYING MENTAL STRESS INDUCED MYOCARDIAL ISCHAEMIA

6.5.1 Haemodynamic responses and mental stress

The haemodynamic response to mental stress typically involves increased heart rate and blood pressure, the latter being sustained by raised systemic vascular resistance, cardiac output, or a combination of the two. Since myocardial ischaemia in this circumstance is triggered by elevated myocardial oxygen demand, and raised rate-pressure product, one possibility is that MSIMI is sustained by the same haemodynamic mechanisms that underlie exercise stress ischaemia.

Compared with exercise there is much lesser rise in HR during mental stress but comparable rises in systolic blood pressure generally giving a lower RPP. There tends to be a greater rise in diastolic blood pressure seen with mental stress compared to exercise [472]. The normal ejection fraction response to exercise is to increase by about 10% [497]

whereas as we have seen the normal ventricular response to mental stress is variable but decreases in a sub-group of patients. Mental stress induces haemodynamic changes much more rapidly than exercise. LV dysfunction happens quickly at a mean of only 49 seconds after the start of stress [497]. This may mean that there is less of a warm up period and that ischaemia is more likely to happen at a lower work load. It has been suggested that this rapid change in BP with acute mental stress, as opposed to the more gradual changes with exercise may play a part in the pathophysiology of plaque rupture [498]. When both ECG changes and decreased left ventricular function co-exist, the ECG changes occur subsequent to changes in ventricular function.

Although there have been exceptions [481], the large majority of studies have demonstrated that myocardial ischaemic responses to mental stress occur at a lower rate-pressure product than exercise-induced ischaemia in the same individual patients [472 499-501]. For example, Goldberg *et al* [482] reported that a speech task elicited myocardial ischaemia at an average rate-pressure product of 6800 (S.D. 3500), compared with 13200 (S.D. 5400) for exercise. The CAD patients who displayed MSIMI in Rozanski *et al*'s study [472] had a mean rate-pressure product during mental stress of 11297 (S.D. 1875), and 17465 (S.D. 3484) during exercise. These findings clearly indicate that the mechanisms underlying MSIMI differ from those implicated in responses to exercise.

Results comparing the haemodynamic responses to mental stress of patients who do and do not exhibit MSIMI have been less consistent. A number of studies involving radionuclide ventriculography have found that the cardiovascular responses to stress are greater in individuals who become ischaemic [482]. Thus a secondary analysis of Rozanski *et al* [472]showed that patients who displayed severe wall motion abnormalities during

speech and Stroop tasks showed greater systolic blood pressure and rate-pressure responses to tasks than did non-ischaemic patients [502].

Similar results have been reported by others [482 485]. In a study that defined abnormal cardiac responses in 168 non-medicated post-infarction patients by ST-segment changes and/or dysrhythmia, clear associations between blood pressure and heart rate responses and cardiac dysfunction were also observed [503]. By contrast, no associations between MSIMI and blood pressure or heart rate responses to stressors have been observed in studies using the nuclear VEST in patients with CAD[471 504] or healthy volunteers[505]. Patients with MSIMI also demonstrate a greater haemodynamic reactivity to exercise. Upon treadmill testing they have a higher RPP, shorter exercise duration, lower RPP at their ischemic threshold and greater ST depression at peak exercise [477 481 502 506].

One factor that may be relevant is the nature of the haemodynamic adjustment underlying the increase in blood pressure. Consistent associations between increased systemic vascular resistance and the development of ischaemia during mental stress tests have been identified [482 484]. The observation that ejection fraction responses to mental stress are negatively correlated with systemic vascular resistance responses indicates that MSIMI might be due in part to an increase in afterload caused by peripheral vasoconstriction. By contrast, systemic vascular resistance is reduced with exercise [482]. Jain *et al* [484] noted that systemic vascular resistance during mental stress increased in patients with CAD and decreased in healthy controls. It is interesting that in a study of healthy volunteers in which a substantial number showed left ventricular ejection fraction decreases of ≥5%, the changes in systemic vascular resistance were also negatively correlated with ejection fraction responses [486]. Thus both in people with and without CAD, mental stress-induced ischaemia is associated with increases in systemic

vascular resistance and afterload. These may be caused by a centrally-mediated neurogenic peripheral vasoconstriction.

A related factor is catecholamine release. Venous adrenaline and noradrenaline increase rapidly with mental stress, and in two studies were larger in men than women [482 486]. The changes in plasma adrenaline were positively correlated with increases in heart rate, systolic blood pressure and rate-pressure product, and weakly negatively associated with systemic vascular resistance [482]. Kuroda *et al* [490] found that increases in adrenaline correlated negatively with changes in ejection fraction during mental stress. However, other studies have shown that MSIMI was not predicted by the rise in catecholamines in patients with CAD [482], although Yoshida *et al* [478] found a greater increase in noradrenaline in patients with vasospastic angina who developed ST segment depression during mental stress.

This inconsistency in associations between catecholamines and stress-induced responses is mirrored in the effects of β-blockade. Bairey *et al* [476] studied the effects of metoprolol or placebo. The impact on MSIMI as defined by wall motion abnormalities was highly variable, with half the patients showing reduced ischaemia while the pattern worsened with metoprolol in a third. In another study, atenolol or nifedipine therapy prevented the fall in ejection fraction found in patients who were positive responders to mental stress, but did not affect ejection fraction in the non-responders [483].

6.5.2 Coronary artery vasomotor responses

Coronary artery constriction and the consequent reduction in myocardial blood flow have been proposed as a cause of MSIMI because of ischaemia occurring at a lower RPP than

exercise. Transient coronary artery occlusion has been witnessed angiographically as a response to mental stress [507]. The catecholamine response to mental stress is predominantly vasoconstrictor but there is an opposing effect due to the release of nitric oxide from healthy endothelium. The normal sympathetically mediated response of the epicardial vessels is alpha-1 mediated constriction which is attenuated by a healthy endothelium possibly via nitric oxide. This may be mediated by a combination of alpha-2 innervation and by flow mediated dilatation.

Recently, cardiac catheterisation studies have used quantitative coronary angiography to assess changes in the diameter of the epicardial coronary arteries during mental stress (see table 6.7). These studies confirm that coronary artery vasoconstriction does occur in response to mental stress, but that changes are highly variable. Yeung *et al* [508]found that in response to mental stress, there was an average 24% constriction in stenotic areas, a 9% constriction of irregular segments, whereas smooth arterial segments did not change overall; the result was a variation across imaged segments from 38% constriction to 29% dilation. Coronary blood flow decreased by 27% during mental stress in patients with stenosed arteries, and rose by an average of 10% in patients with smooth arteries. An association between changes in coronary artery diameter in response to mental stress and acetylcholine was also observed, suggesting a local failure of the endothelium-dependent vasodilator response. By contrast, stenosed and smooth coronary artery segments showed similar dilatation in response to nitroglycerin, indicating no differences in endothelial independent vasodilatation.

There was also substantial variability in coronary vasoconstriction in a larger study in which coronary blood flow was assessed [509]. Coronary flow velocity increased by 32% with mental stress in controls but not in CAD patients, and 18.6% of patients showed

coronary constriction of >0.15 mm, consequently there is an increase in oxygen demand with no increase in flow in a group of CAD patients. However, responses in the epicardial arteries during mental stress varied between 15% constriction and 27% dilation in diseased segments, and from 22% constriction to 12% dilation in smooth segments. The changes in arterial diameter were associated with the magnitude of diastolic blood pressure stress responses, with vasodilatation in low pressure responders, and vasoconstriction in high diastolic pressure responders.

Kop *et al* [509] have argued that the degree of arterial constriction is insufficient to account for the decrease in coronary artery flow measured, and also suggested that there is likely to be a significant contribution from vasomotor changes in the microvascular bed. Dakak et al have reported that the attenuation in coronary arterial blood flow increase during mental stress can be reversed by alpha-adrenergic blockade through intra-coronary administration of the alpha adrenergic antagonist phentolamine[510]. This observation, coupled with the fact that there was no evidence of coronary vasomotion during their study, points to the microvasculature as one area responsible for flow attenuation.

Arrighi *et al* [511] used PET scanning to quantify myocardial blood flow have found the opposite to some other authors. They found that coronary flow reserve during mental stress was lower in regions without significant epicardial stenosis than in those with significant stenosis. In healthy controls, both mental and dipyridamole stress induced increased myocardial blood flow. Microvascular dysfunction may be responsible for the blunted myocardial flow response in regions without significant stenosis. Mazzuero [488] suggested that there may be a dilatation of the normal vessels to allow extra flow at the same time as a decrease in flow in diseased regions.

The results of these studies indicate that MSIMI may be sustained by abnormal responses both in the epicardial coronary arteries and in the microvasculature, and that there may be both an impairment of endothelial function and alpha-adrenergic vasoconstrictive responses.

When assessing the data from the angiographic studies, it is important to bear in mind that the control patients used have a significant amount of co-morbid pathology such as cigarette smoking, diabetes, hypertension and hypercholesterolaemia; all of which affect normal endothelial function.

6.5.3 Psychological and central nervous system factors

Surprisingly little is known about psychological aspects of MSIMI. The phenomenon is induced by emotional threat or challenge, but the latter have seldom been quantified. It is not therefore clear whether the tasks that most reliably induce MSIMI are necessarily the most "stressful"[472]. The few studies that have assessed subjective responses to tasks have demonstrated positive correlations between increases in anger and anxiety and reductions in left ventricular ejection fraction [496], and coronary vasoconstriction [512].

There is some evidence that MSIMI is associated with certain psychological traits. Carels *et al* [513] had patients monitor their levels of subjective tension repeatedly in every day life using diaries, and categorised them into high and low emotional responders. High emotional responders had a greater incidence of wall motion abnormalities compared with low responders on mental stress testing, but emotional responsivity was not linked to myocardial dysfunction on exercise. High emotional responders also had

greater trait anxiety and more depressive symptoms, and were more likely to be diabetic and current smokers. No association with hostility was observed. The more aggression displayed by a subject has also been linked to an increased tendency to ST segment depression during mental stress testing [514]. Alterations in the ratio of peripheral alpha-2 to beta-2 receptor density has previously been documented in young men with type A behaviour and premature coronary artery disease suggesting a mechanism linking this behaviour pattern with vasoconstriction to mental stress [515].

By contrast, another study showed that patients who exhibited MSIMI had higher ratings of aggressive responding, hostile affect, and trait anger than patients who did not show ischaemic responses during mental stress, with no differences in anxiety or neuroticism[471]. Results relating MSIMI with psychological characteristics are therefore inconclusive at present.

The cardiovascular responses to mental stress have cerebral correlates as identified using PET scanning, with increased blood flow to the right anterior cingulated gyrus, right insula and cerebellar vermis, and reduced blood flow in the prefrontal and medial temporal cortex in healthy individuals[516]. In one study coupling brain PET scanning with echocardiography, CAD patients who exhibited wall motion abnormalities during mental stress showed heightened regional cerebral blood flow to the left hippocampus and inferior parietal lobe, left frontal gyrus and visual association cortex, and reduced flow to the anterior cingulated and right middle and superior frontal gyri [517]. This suggests that MSIMI may be driven by abnormal patterns of cerebral cortical activation.

6.6 CLINICAL SIGNIFICANCE OF MENTAL STRESS – INDUCED MYOCARDIAL ISCHAEMIA

6.6.1 Association with severity of coronary artery disease

The majority of studies have shown no link between the angiographic severity of coronary artery disease and the presence of mental stress ischaemia [470 481 484 485 502 506]. Kuroda *et al* [490] reported a trend towards greater decreases in ejection fraction during mental stress in patients with three vessel disease, while the rate of MSIMI in Modena's[473] study varied from 54% in patients with one vessel disease to 83% in three vessel disease. However, interpretation of this finding is complicated by the unknown medication status of participants. Studies relating thallium reversibility scores on a prior radionuclide examination with the subsequent incidence of MSIMI have reported variable results [484 504]. It would appear therefore, that transient stress-induced ischaemia is not simply a reflection of disease severity, but an indicator of a particular susceptibility to psychological factors. This lack of association with angiographic disease severity underlines the fact that MSIMI is likely to be a dynamic functional phenomenon as opposed to a simple question of flow limitation. This reinforces the proposed underlying mechanism of coronary artery constriction in its pathogenesis.

6.6.2 Laboratory mental stress and ambulatory ischaemia

Ambulatory myocardial ischaemia has parallels with mental stress-induced ischaemia in that both are predominantly silent events, and occur at lower heart rates than exercise-induced ischaemia. They also both occur largely in patients who also experience exercise-induced ischaemia. It has been proposed that mental stress in everyday life is an important determinant of ambulatory ischaemia [353 354]. Several studies have therefore assessed both MSIMI and ambulatory ischaemia, and have found associations between

the two [470 475 485 518-520]. For example, in the PIMI study, it was found that 49.4% of patients who displayed myocardial ischaemia in response to a speech task in the laboratory had ambulatory ischaemia during Holter monitoring, compared with 34.9% of the remainder[475]. They also experienced more frequent and longer ambulatory ischaemic episodes, but did not show differences in clinical markers of disease severity. The proportions of patients showing ambulatory ischaemia in Legault's[521] series were 68.4% and 37.0% for MSIMI positive and negative groups respectively, and the ejection fraction response to mental stress was a significant predictor of ambulatory ischaemia independently of left ventricular responses to exercise. The frequency and duration of episodes of ambulatory myocardial ischaemia is also predicted by the magnitude of heart rate responses to mental stress tests [520]. This again emphasises the importance of stress reactivity. Gottdiener *et al* [470] compared 24 CAD patients who showed new wall motion abnormalities on mental stress testing with 21 who did not. The duration of ischaemia while the patients were sedentary was 22.9 min in the MSIMI positive group, and 3.6 minutes in the negative group. In combination, these data suggest that clinical mental stress testing may index triggers of myocardial ischaemia that are also operative in everyday life.

6.6.3 The prognostic significance of mental stress-induced ischaemia

Several of the groups of CAD patients whose sensitivity to mental stress has been evaluated have been followed up to assess the prognostic significance of a positive ischaemic response. All the results published to date have indicated that MSIMI is a predictor of poor prognosis. Specchia *et al* [481] tracked 61 patients who showed signs of MSIMI, and 211 who did not, over an average of 51 months. The two groups did not differ in severity of CAD or left ventricular function. Over the follow-up period, 65.5%

of the positive mental stress group underwent revascularization (coronary artery bypass survey or angioplasty), compared with 38.3% in the comparison sample. These figures must be interpreted with caution though as end-points such as revascularisation or unstable angina (if not defined by ECG or enzyme criteria) may well be symptom driven and perception of symptoms may be affected by mental stress. A 12 month follow-up of 30 high risk patients originally studied using the nuclear VEST[471] found that 60% of MISMI-positive patients had experienced a nonfatal myocardial infarction, cardiac death or unstable angina requiring hospitalization, compared with 20% of the MSIMI-negative group[522]. Jiang *et al* [519] tracked 126 patients over 44 months, and found adverse events (death, nonfatal myocardial infarction or revascularization) in 27.4% mental stress-positive and 11.9% stress-negative patients. The difference was not accounted for by differences in risk profile, and was independent of age, history of myocardial infarction, and baseline ejection fraction. Mental stress-induced ischaemia also predicted adverse outcomes independently of other risk factors over an average 42 months in a group of 79 patients originally tested using radionuclide ventriculography or echocardiography[518]. Most recently, the PIMI cohort of 196 patients with CAD was reviewed an average of 62 months after mental stress testing [523]. The all cause mortality rates were 16.2% in mental-stress positive and 6.6% in mental stress-negative patients, a difference that remained significant after adjusting for age, history of myocardial infarction and diabetes, baseline ejection fraction, hypertension, and duration of exercise tolerance tests. Although the numbers of patients followed up so far are small, current evidence suggests that myocardial ischaemic responses to standardised mental stress are clinically significant, relating both to ambulatory ischaemia and to prognosis.

6.7 Limitations in the literature and unresolved issues

As noted in Tables 6.1-6.6, mental stress testing has been carried out most commonly in men, and the numbers of women tested has been too small to allow comparisons to be made. Men and women may differ in their cardiovascular responses to mental stress [524]. Bairey Merz *et al* [525]found that women had greater blood pressure, heart rate and rate-pressure product responses to mental stress than men, and that the difference was enhanced among post-menopausal women. It has also been noted that mental stress induced ischaemia is more likely to be associated with chest pain in female than male CAD patients [526], and levels of plasma β-endorphin are also lower. In healthy volunteers without CAD, left ventricular ejection fraction decreases during mental stress were greater in women than men [486]. However, there is insufficient information to draw firm conclusions about the prevalence and significance of MSIMI in women with CAD.

An important limitation in the current literature is the lack of data concerning the duration of stress-induced ischaemic responses. In most studies, comparison have been made between images or measures obtained at baseline, and then during or immediately after mental challenge. Responses may be transient, but it is not clear how long they last. One study suggests that the decreases seen in LV function persist during mental stress testing but that ventricular function rapidly returns to its original state post test [497], however there are few other data in this area.

Recent studies indicate that brief mental stress stimulates impairments in vascular endothelial function that last for up to 90 minutes after the termination of stress[154]. Similarly, increases in inflammatory cytokine concentration evolve over several hours

[527]. It is possible, therefore, that disturbances of myocardial function are also sustained after mental stress tests are completed.

Many of the studies in the literature involve small numbers of patients, and there have been no control groups in several instances. In a number of studies, the controls have been patients under investigation for heart disease; although they were free of CAD, they may have had other cardiovascular conditions, so their results may not have been representative of the healthy population. The preponderance of studies have found evidence of MSIMI, and publication bias in favour of positive results cannot be ruled out.

Finally, there is a growing literature concerning other aspects of psychophysiological response in patients with CAD, highlighting the possibility of differences in stress-related disturbances of autonomic balance [213], endothelial function, and platelet activation [359]. These observations have yet to be integrated with research on mental stress-induced ischaemia. Transferring the pathophysiological findings into clinical practice will need more information on both the independent prognostic significance of the mental stress-induced myocardial ischaemia, and the possibility of altering the underlying pathophysiological mechanisms by specific pharmacological or psychological interventions. Such information is currently sparse.

6.8 CONCLUSIONS

Mental stress induces transient myocardial ischaemia in one third to one half of patients with CAD. Ischaemic responses are induced not only by extremely severe emotional stress, but by behavioural challenges similar to those that might be encountered in

everyday life, and they are associated with ischaemia on ambulatory monitoring. Mental stress-induced ischaemia is typically without pain, and occurs at lower levels of oxygen demand than ischaemia induced by physical exercise. It is generally not related to the severity of CAD. Mental stress-induced haemodynamic changes, particularly increases in systemic vascular resistance, coronary artery vasoconstriction, and microvascular changes, may all contribute to the pattern of ischaemia. The psychophysiological reactivity to stress may be important, it is linked to the development of mental stress induced ischaemia but also to the presence of coronary vasoconstriction and the presence of ambulatory ischaemia. There is, nonetheless, considerable variability in responses to mental stress that is not understood. No pharmacological interventions have yet consistently blocked mental stress-induced ischaemia. Limited evidence indicates that these stress-induced responses predict adverse coronary outcomes independently of risk factors. It may be premature to advocate that mental stress testing forms an integral part of the routine clinical investigation of patients with suspected or proven CAD, but mental stress testing may provide a means of evaluating the role of emotional factors in acute coronary syndromes and sudden cardiac death.

Table 6.1. Studies using ECG assessments of mental stress induced myocardial ischaemia

Author	Patients	Mental Stressor	Medication (on / off)	Mental stress induced myocardial ischaemia (MSIMI)	Other results
Schiffer[501]	36 angina pectoris sex not stated	Quiz	Off	33%	ST segment depression criterion ≥1mm All patients showing MSIMI were ischaemic on exercise test at a higher rate-pressure product than during mental stress
Specchia [506]	**122 chest pain patients** mostly men	MA	Not stated	18%	ST segment depression criterion ≥1mm Same proportion (18%) of patients with and without significant stenosis on angiography show MSIMI
Jennings[480]	11 CAD 11 controls All men	MA, RT, combined RT and MA	Off	55%	ST segment depression criterion ≥1mm No MSIMI in controls
L'Abbate[499]	50 CAD mostly men	MA	Off	44%	Criteria: ST segment depression ≥0.1 mV, or ST elevation ≥0.15 mV MSIMI at lower rate-pressure product than with exercise in 73% of cases
Specchia[481]	372 angina pectoris mostly men	MA	Off	16%	ST segment depression criterion ≥1mm In patients showing MSIMI, the rate-pressure product threshold for ischaemia is similar for exercise and mental stress
Kral [479]	152 siblings of patients with premature CAD	Stroop	off	0%	ST segment depression criterion ≥0.1mm
Wong [477]	35 CAD mostly men	MA, Speech, Stroop, computer game	On	12%	ST segment depression criterion ≥0.1mV No association with severity of coronary disease.

Author	Patients	Mental Stressor	Medication (on / off)	Mental stress induced myocardial ischaemia (MSIMI)	Other results
Yoshida[478]	**29 vasospastic angina** men and women	MA	Off	28%	ST segment depression criterion ≥0.1mV Patients with coronary artery stenosis excluded

Mostly men: >75% male participants. MA :mental arithmetic. RT: reaction time task. Stroop: colour/word interference task.

Table 6.2. Studies using radionuclide ventriculography without perfusion assessment to assess mental stress induced myocardial ischaemia

Author	Patients	Mental Stressor	Medication (on / off)	Mental stress induced myocardial ischaemia (MSIMI)	Other results
Rozanski[472]	39 CAD 12 controls Mostly men	MA, Speech Stroop	Off	59% patients (WMA) 36% patients (LVEF) 8% controls (WMA)	WMA developed in 74% with exercise LVEF criterion ≥5% decrease
LaVeau[497]	9 CAD 7 controls All men	MA, Speech, Stroop	some on some off	Not stated	CAD: LVEF fell by 2 % with MA, 1% with Stroop, and 3 % with PS Controls: LVEF rose by 6% with MA, 13% with Stroop and 6% with PS
Bairey [476]	19 CAD mostly men	MA, Speech, Stroop,		74% (placebo) 64% (metoprolol)	MSIMI defined as worsening wall motion abnormality
Ironson[496]	18 CAD 9 controls All men	MA, Speech anger recall	Off	44% patients (WMA) 39% patients (LVEF) 11% controls (LVEF)	LVEF criterion ≥7% decrease
Miller[500]	33 CAD Men and women	Speech	some on some off	33% (WMA) 15% (LVEF)	LVEF criterion ≥5% decrease
Blumenthal[485]	132 CAD Mostly men	MA, MT, Speech, interview	Off	34% (WMA)	49% show WMA with exercise
Krittyayaphong [520]	53 CAD Mostly men	Speech	some on, some off	50% (WMA and/or LVEF)	LVEF criterion ≥5% decrease
Jiang[528]	47 CAD Mostly men	Speech	Off	21%	MSIMI defined as new wall motion abnormality MSIMI less common in patients who were physically fit

Author	Patients	Mental Stressor	Medication (on / off)	Mental stress induced myocardial ischaemia (MSIMI)	Other results
Goldberg [482]	196 CAD Mostly men	Speech, Stroop	Off	58%	MSIMI defined as ST-segment depression, and/or new or worsening WMA, and/or LVEF decrease > 8%. New WMA and reduction in LVEF correlated with increase in systemic vascular resistance during mental stress.
Becker[486]	29 healthy volunteers men and women	Speech, Stroop	None	10% (WMA) 41% (LVEF)	LVEF criterion ≥5% decrease (17% with ≥8% decrease) Change in LVEF during mental stress inversely associated with change in systemic vascular resistance
Jain[484]	21 CAD 9 controls Mostly men	MA, anger recall	On	43% patients (LVEF) 33% patients (WMA) 33% controls (LVEF)	LVEF criterion ≥5% decrease Change in LVEF during mental stress inversely associated with change in systemic vascular resistance
Andrews[483]	18 CAD mostly men	MA, Stroop, interview	On	53% (WMA) 31% (LVEF)	LVEF criterion ≥5% decrease Pharmacological study: WMA prevented by nifedipine or atenolol
Hunziker[529]	10 CAD 11 controls men and women	MA	Not stated	Not stated	Combined mental and physical stress leads to slightly greater decrease in LVEF, but similar haemodynamic response, to exercise alone
Bairey Merz[525]	58 CAD 42 controls Mostly men	MA, Speech Stroop	Off	64% patients (WMA) 12% patients (LVEF) 10% controls (LVEF)	LVEF criterion ≥5% decrease

Mostly men: >75% male participants. MA :mental arithmetic. Stroop: colour/word interference task. LVEF: Left ventricular ejection fraction. WMA: wall motion abnormality

Table 6.3. Nuclear studies of mental stress induced myocardial ischaemia assessing perfusion

Author	Patients	Mental Stressor	Medication (on / off)	Mental stress induced myocardial ischaemia (MSIMI)	Other results
Mazzuero [488]	10 post MI mostly men	MA	Off	70% (scintigraphy) 67% (WMA)	Scintigraphy criterion: reversible segmental hypoperfusion
Bosimini[489]	37 post MI 22 controls all men	MA	Off	89% (scintigraphy) 22% (ECG) 0% control	Scintigraphy criterion: reversible myocardial hypoperfusion ST segment depression criterion ≥0.1mm
Kuroda[490]	20 CAD Mostly men	MA	Off	100% (scintigraphy) 60% (WMA) 50% (LVEF) 30% (ECG)	LVEF criterion ≥5% decrease ST segment depression criterion not stated

Mostly men: >75% male participants. MA :mental arithmetic. Stroop: colour/word interference task. LVEF: Left ventricular ejection fraction. WMA: wall motion abnormality

Table 6.4. Echocardiographic studies of mental stress induced myocardial ischaemia

Author	Patients	Mental Stressor	Medication (on / off)	Mental stress induced myocardial ischaemia (MSIMI)	Other results
Modena [473]	31 CAD 25 no CAD mostly men	MA	Not stated	61% CAD 8% no CAD	Patients assessed during diagnostic coronary arteriography MSIMI defined by wall motion abnormality Rate of MSIMI varies from 54% (one diseased vessel) to 83% (3 diseased vessels)
Gottdiener[470]	45 CAD 12 controls All men	MA, Speech	Off	53% CAD 0% controls	MSIMI defined as new wall motion abnormality No relationship with number of diseased vessels
Soufer[517]	10 CAD 6 controls All men	MA	Not stated	33% CAD 0% controls	MSIMI defined as new or worsening wall motion abnormality Study carried out in combination with cerebral PET scanning. Cortical activation associated with MSIMI
Okano[530]	7 CAD 8 no significant CAD men and women	MA	Not stated	0%	MSIMI defined by wall motion abnormality or reduced LVEF

Mostly men: >75% male participants. MA :mental arithmetic. LVEF: Left ventricular ejection fraction

Table 6.5. Nuclear VEST studies of mental stress induced myocardial ischaemia

Author	Patients	Mental Stressor	Medication (on / off)	Mental stress induced myocardial ischaemia (MSIMI)	Other results
Breisblatt[492]	35 post MI mostly men	MA, Stroop,		37%	LVEF criterion ≥5% decrease
Young[531]	12 healthy volunteers all men	MA, Interview	Off	17%	LVEF criterion ≥5% decrease
Bairey [505]	18 healthy volunteers Mostly men	MA, Speech, Stroop	Off	22%	LVEF criterion ≥5% decrease Similar blood pressure and heart rate responses in participants with and without MSIMI
Burg[471]	30 CAD Sex not stated	MA, Interview Reaction time	On	60% (interview) 50% (MA)	LVEF criterion ≥5% decrease Similar blood pressure and heart rate responses in participants with and without MSIMI. No LVEF decrease in response to reaction time task. No association between LVEF decrease and severity of CAD
Legault[504]	47 CAD 20 controls All men	Speech	mostly off	49% (CAD) 0% (Control)	LVEF criterion ≥5% decrease
Vassiliadis[532]	8 CAD 8 controls all men	Video game	Off	62% (CAD) 25% (Control)	LVEF criterion ≥5% decrease

Mostly men: >75% male participants. MA :mental arithmetic. Stroop: colour/word interference task. LVEF: Left ventricular ejection fraction

Table 6. 6 Studies of mental stress induced myocardial ischaemia using Positron Emission Tomography

Author	Patients	Mental Stressor	Medication (on / off)	Mental stress induced myocardial ischaemia (MSIMI)	Other results
Deanfield [474]	16 CAD 13 controls All men	MA	Not stated	75% (PET) 38% (ECG)	PET ischaemia defined as abnormal regional myocardial perfusion ST segment depression criterion ≥0.1mm
Benight [533]	6 CAD 9 controls All men	Anger recall	On		No evidence of decreased perfusion in CAD patients Greater perfusion in healthy coronary artery segments from controls than in diseased segments in CAD patients
Arrighi[511]	10 CAD 5 controls Gender not stated	Not stated	On		Coronary flow reserve during mental stress lower in regions without significant epicardial stenosis than in those with significant stenosis. Increase in myocardial blood flow blunted in regions without epicardial stenosis.
Schoder[495]	17 CAD 17 controls Men and women	MA	Off		Myocardial blood flow increases with mental stress in CAD and controls, but rise is greater in controls In regions with fixed perfusion defects, myocardial blood flow does not increase. Coronary resistance similar in the two groups at rest, but fell in controls and was unchanged with mental stress in CAD.
Schoder [494]	24 controls Men and women	MA	Off		Increase in myocardial blood flow and decrease in coronary resistance with mental stress, correlated with increases in catecholamines and rate-pressure product

MA :mental arithmetic

Table 6.7. Studies of mental stress induced myocardial ischaemia using coronary angiography

Author	No. patients	Mental Stressor	Medication (on / off)	Results
L'Abbate[499]	10 CAD 3 no significant CAD sex not stated	MA	Off	No change in normal or diseased coronary artery segments with mental stress
Yeung[508]	15 CAD 11 controls men and women	MA	Not stated	Diseased segments of coronary arteries constrict during mental stress, with dilatation in smooth segments. Responses vary from 38% constriction to 29% dilatation
Boltwood [512]	12 CAD all men	Anger recall	Off	Positive correlations between anger responses and coronary vasoconstriction of diseased segments
Dakak [510]	10 CAD 5 controls mostly men	Computer game	Off	Blood flow measured in LAD artery – none of the patients have significant disease in this vessel. Vascular resistance in LAD decreases during mental stress in controls, but not in CAD patients. Pharmacological interventions suggest an α-adrenoreceptor mediated effect
Lacy[534]	6 CAD 5 controls mostly men	Speech	Off (although diazepam sedation)	Average 6% decrease in coronary artery diameter during mental stress both in CAD patients and controls
Kop [509]	59 CAD 17 controls mostly men	MA	Off	18.6% show coronary constriction > 0.15 mm during mental stress Coronary blood flow increases in controls but not CAD during mental stress

Mostly men: >75% male participants. MA :mental arithmetic

Chapter Seven

THE ACCENT (ACute Coronary syndrome: EmotioN and Trigger) STUDY

OBJECTIVES, PATIENTS AND METHODS.

7.1 INTRODUCTION

The involvement of psychosocial factors in the aetiology of acute cardiovascular disease, from their role in atherogenesis to triggering of acute events, has been detailed Chapters 3, 5 and 6. However, when analyzing the current literature there are several important questions as yet left unanswered regarding the pivotal role that psychosocial factors may play in the triggering of ACS in some patients.

Much of the data have described findings for the trigger period only, without any comparison or consideration of habitual rates of exposure to triggers. The two major publications providing controlled data on psychological factors as acute triggers of coronary events are the Onset Study [115] and the SHEEP study [316]. Both of these have given us valuable information about the incidence of anger as a trigger of ACS but do not tell us several important things.

Both studies have only looked at proven AMI and have ignored the group of patients with the part of the ACS spectrum previously diagnosed as unstable angina [17]. As discussed in chapter 2, the way that acute coronary disease is classified has changed over the last few years and it is germane to current clinical practice that an assessment is made

on the most up-to-date clinical criteria endorsed by the European Society of Cardiology and the American College of Cardiology [17]. This group is likely to include a significantly greater number of cases with the new diagnosis of NSTEMI which were previously diagnosed as unstable angina or did not meet diagnostic criteria [18]. When these previous studies were performed, troponin assays were not in widespread clinical use. Now with the use of these sensitive biochemical markers of myocyte necrosis it is easier to identify these ACS patients with NSTEMI as evidenced by troponin positivity in the absence of dynamic ECG changes, allowing us to examine a wider spectrum of acute coronary disease. Patients with positive troponin assays in the absence of diagnostic ECG changes now form a considerable part of the workload of acute cardiovascular disease, and so it is important to study this entire group comprising the range of ACS in contemporary practice.

Previously, all AMI that have been examined have been grouped together with respect to their ultimate ECG diagnosis, rather than by presenting features. Neither the MILIS [254] or SPRINT [309] studies or the study by Miric[310] et al did any analysis on the difference between STEMI and NSTEMI, and like most of the observational studies examining circadian variation in AMI onset, they tended to look at Q-wave versus non-Q-wave infarction; this was the favoured method of infarct classification at the time, but has now been superceded by STEMI versus NSTEMI [17]. Whereas the presence of Q-waves is a broad surrogate of severity of infarction, the diagnosis of STEMI or NSTEMI has important ramifications for the acute treatment received by the patient at presentation as well as on the short and medium term prognosis.

Mittleman et al [115] used creatine kinase measurement as an inclusion criterion, and all infarcts (whether STEMI or NSTEMI, Q-wave or non-Q wave) were considered

together. The SHEEP study by Moller et al [316] also analysed the data in this way and paid no attention to clinical or electrocardiographic correlates. Having considered some of the potential underlying linking mechanisms (see chapters 3 and 5) between psychological factors and CAD, it is conceivable that psychosocial factors could influence the ECG presentation of ACS. For example, the presence of anger as an acute trigger, as well as precipitating plaque rupture may also predispose the patient to increased coronary arterial tone and hypercoagulability, giving rise to total vessel occlusion and a more severe presentation and prognosis. This may be reflected either in the ECG findings or by greater release of biochemical markers of myocyte necrosis (creatine kinase or troponin). There are currently no data correlating these markers and trigger factors. Importantly, there are very little data on the subject of the demographic, social and clinical correlations of psychosocial triggers and no information on prognosis.

The SHEEP study [316] only looked at first events of non-fatal myocardial infarction. The Onset study [115] looked at all-comers with 29 of patients (out of 1623) in that study having had a previous myocardial infarction. The whole spectrum of ACS is clinically important and so patients with previous ACS and previous revascularization procedures were also included in our ACCENT study population. Thus this study has the ability to look at the full spectrum of acute coronary syndromes which has not been done before.

The data that we have regarding the overall incidence of triggers have largely come as a by-product of other studies looking at myocardial infarction. Apart from the Onset [115] and the SHEEP [316] studies, none of the observational studies have attempted to separate out the experience of anger, stress and depression as acute aetiological factors but have considered only "stress" as a causal factor. Most of the data have no control or comparison period, so may not reflect habitual exposure and may not be a true reflection

of true "triggering" of ACS. Although depression is strictly a chronic condition, it is of interest to see the influence of acute depressive symptoms on the incidence of ACS onset.

Physiological and biochemical factors have an important effect on the acute clinical course of the ACS and also play a role in the short and long-term prognosis of the patient. There are few data on correlations between these and either ACS trigger factors or psychosocial factors. Consequently it is not only of great academic interest but of significant public health interest to see the way in which acute psychological factors may influence the clinical presentation and course of ACS.

7.2 OBJECTIVES

It was hypothesized that psychosocial factors would trigger the onset of ACS in a proportion of patients, as well as influence the clinical findings at presentation. Consequently we designed the ACCENT study with several goals in mind

1. To assess the incidence of trigger factors (including physical exertion, smoking and negative emotional states) prior to ACS onset, and relate these to new diagnostic criteria.

2. To examine the link between psychosocial triggers and the electrocardiographic manifestations of ACS.

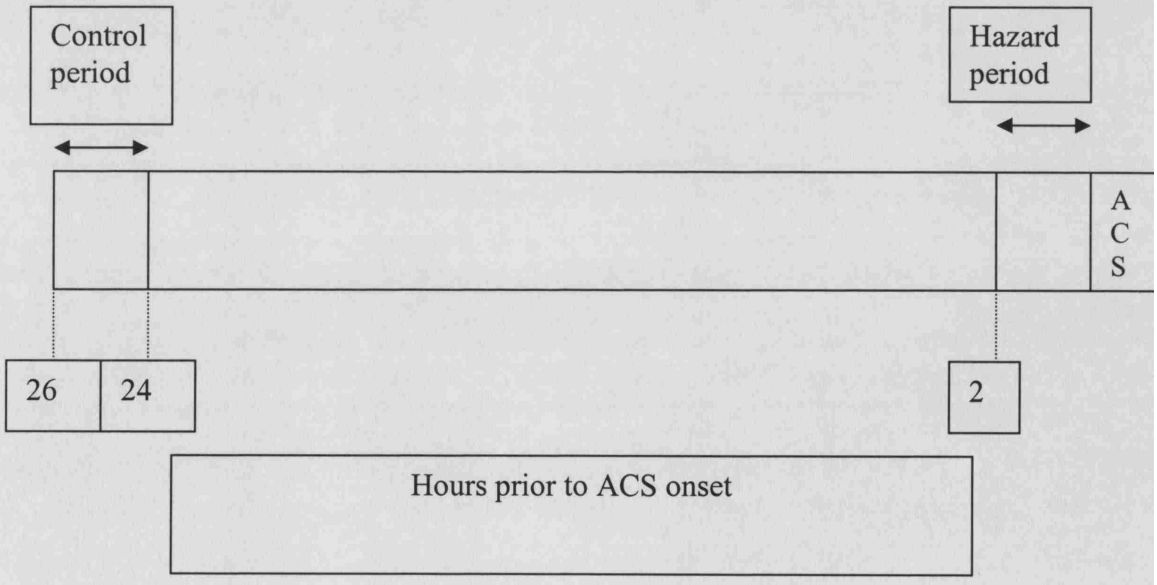
3. To find out whether particular types of ACS patient are especially susceptible to triggers.

4. To assess whether trigger factors are associated with particular clinical and laboratory findings at ACS presentation and subsequent hospital admission.

5. To discover whether the experience of stress, anger and depression in the period immediately preceding ACS onset can be differentiated.

On the basis of the literature, we define the hazard period for triggers as the two hours before onset of ACS initiation by chest pain. Data were collected separately in relation to both hours in the hazard period; the first hour of the two hour period (1st hour) and also the hour immediately before onset before ACS onset (2nd hour). In addition, the two hours were aggregated in several analyses (combined hazard period).

Figure 7.1 Schematic representation of the case-crossover study time periods (adapted from Mittleman et al[115]).



7.3 PATIENTS AND METHODS

7.3.1 Patients

Patients were recruited from the coronary care units of University College Hospitals NHS trust, St. George's Hospital (both London), and Southend Hospital, Essex. Approval for the study was given by the medical directorate, the Ethics Committee, and the Research and Development Committee at each establishment. There was also close liaison with the individual clinicians responsible for the coronary care units and care of acute cardiac patients at each site.

Dates of recruitment were:-

University College Hospitals NHS trust	01/10/01 to 01/08/04
St. George's Hospital	01/09/02 to 01/08/04
Southend Hospital	01/02/02 to 06/01/03

Admissions to these coronary care units were screened for inclusion. There were a total of three researchers involved in patient recruitment; myself, 1 post doctoral heath psychologist and one senior cardiac nursing sister working on a doctoral thesis. Non-medically trained researchers received training in ECG interpretation and in the medical background to the study although they were blinded to the study hypotheses. Researchers were not available to attend all departments on a daily basis so not all admissions were assessed for suitability for inclusion into this study. Consequently it was not possible to keep a diagnostically accurate registry of all admissions during that

period. Potential study candidates were identified by examination of medical notes of patients with a possible diagnosis of ACS according to the nursing staff or ward Kardex system.

All patients were required to have had a specific time of onset of chest pain and to be able clearly to recall the circumstances surrounding this event to ensure accurate information regarding the trigger period. The diagnosis of ACS was made on the presence of chest pain plus verification by either diagnostic ECG changes [17](ECG criteria being new ST elevation of > 0.2mV in 2 contiguous leads in leads V1, V2 or V3 and of > 0.1mV in 2 contiguous other leads, ST depression of > 0.1mV in 2 contiguous leads in the absence of any QRS confounders, new left bundle branch block or dynamic T wave inversion in more than one contiguous lead), troponin T measurement of > 0.1 μg/l, or a creatine kinase measurement of over twice the upper range of normal for the measuring laboratory. Fixed T wave inversion in the absence of positive biochemistry was not included.

There are many causes of a false positive troponin T assay, and it has been suggested that the new third generation troponin T test has a clinically relevant cut-off point of about 0.1μg/l [535]. Although some clinicians now consider a value of > 0.03μg/l to be diagnostic, because of concerns at the time of setting up the protocol about the diagnostic accuracy of Troponin T at mildly elevated levels (i.e. 0.03 – 0.1μg/l), we followed the lead of the clinical cardiology services at our main recruiting centre and used the Troponin level of > 0.1 μg/l as the diagnostic cut off point for ACS in the absence of ECG changes. This may mean that there have been a small number of patients with marginally raised troponin levels and non-diagnostic ECGs who have been excluded from the study. Consequently although this decreased the sensitivity of the study, the

specificity was increased. Because of the need to focus on the influence of trigger factors, strict exclusion criteria in patient selection were established to minimize possible confounding factors.

7.3.2 Exclusion criteria

1. Absence of an identifiable onset time of pain to allow recall of factors leading up to it.
2. Patients who were unable to recall events clearly
3. Patients with ongoing critical ischaemia
4. Patients too ill for successful interview
5. Patients whose short/medium term outlook was compromised by other conditions,
6. Patients with unexplained anaemia (haemoglobin less than 12.0 g/dl) or renal failure (creatinine greater than 150 mmol/l)
7. Patients with active or recent (within one month) episodes of infection or surgery
8. Patients within 3 months of an acute coronary syndrome, coronary angiography, angioplasty or coronary artery bypass grafting.
9. Patients with ongoing infection, inflammatory conditions or neoplastic illness
10. Patients presenting with severe pulmonary oedema
11. Patients under 18 years (because of consent issues) or over 80 years of age (because of the likely presence of occult co-morbid pathologies).
12. Patients with stuttering or insidious onset of symptoms preventing proper use of the case-crossover method.
13. Patients with severe psychiatric illness
14. Finally, because of the need to understand and complete a detailed interview and psychometric questionnaires patients not fluent in English were also excluded.

Any patients in whom there was doubt about suitability for study inclusion had their cases reviewed by a cardiologist either at the referring site or by myself.

7.3.3 Patient Recruitment and rationale for exclusions

All suitable identified patients were invited to participate in the study. The study was explained verbally to participants and they were then given a patient information sheet (see appendix i) explaining the rationale behind the study and the implications of their involvement. Patients were allowed 10 minutes to read the patient information sheet and to think about participation in the study. They were then given the opportunity to ask questions. A brief conversation took place to ensure that they could accurately recall the time of onset of their chest pain and that they had no exclusion criteria. Patients who wished to participate were then asked to sign a consent form (see appendix ii). One copy of the consent form was retained by researchers, one copy was placed in the hospital notes and a third copy was given to the patient themselves.

The timing of onset of symptoms is obviously one of the fundamental cornerstones of the study. To make things as accurate as possible we just dealt with patients who had had chest pain as their initiating symptom as symptoms such as breathlessness may not necessarily relate to the onset of ACS but to secondary heart failure or other pathologies. The time of chest pain onset was taken as the time of the start of the ACS. We included patients who had had premonitory symptoms over the preceding days or weeks, provided there was an obviously worst episode of pain accompanied by dynamic ECG changes that could be defined as the definite onset.

Specific areas which we examined closely were the patient's accurate recollection of the timing of chest pain onset and the circumstances surrounding it, and inability to clearly recall events precluded admission to the study. It was also important to try and ensure that apart from their coronary artery disease that patients had no other significant co-morbid medical conditions which may theoretically affect the acute CAD disease process, affect assessment of the haematological and biochemical results, or that might have effects on mood or psychological functioning. This is the reason why patients with unexplained anaemia or renal failure were excluded (criterion 6), as anaemia may reflect occult malignancy, haematological disorder or make patients more susceptible to myocardial ischaemia. Renal failure as well as representing occult disease may cause troponin false positivity. Patients with active or recent episodes of infection, surgery, neoplasia or inflammation were similarly excluded (criteria 7 and 9). Patients with recent ACS or coronary intervention procedures were excluded because of the accepted complication rate of these conditions within the first 3 months (criterion 8). Patients over the age of 80 were excluded because of concerns about occult medical problems influencing the presentation of ACS as well as serological markers and accuracy of event recall; persons under the age of 18 were excluded for consent reasons and the low likelihood of an apparent ACS being due to atherosclerotic coronary artery disease (criterion 12). Patients who were unstable or too ill were not included as it was felt unreasonable to subject these people to interviews including recall of potentially emotionally charged events (criteria 3 and 4) . Patients with severe pulmonary oedema were not included for reasons of difficulty of interviewing patients with breathlessness as well as the effect of pulmonary oedema on markers such as troponin and CRP (criterion 10) . Finally patients with severe psychiatric illness were excluded because of concerns about the accuracy of reporting events and the effects of illness such as depression on biochemical markers [87] (criterion 14) .

7.4 DATA COLLECTION

7.4.1 Patient Demographics

Information was collected from the patient notes and observation charts. Details were verified with the patient. The information derived from the patient notes included name, address, telephone number, date of admission, date of birth, gender, height and weight. There details were then corroborated with the patient.

7.4.2 Blood results

Blood results were taken from the hospital computerised record of pathology results. All blood tests recorded were those taken by the admitting physicians at the immediate time of the patients admission with the exception of troponin T and creatine kinase levels in which case the highest value obtained on that admission was recorded. Not only are troponins and cardiac enzymes valuable diagnostic tools in the identification of ACS but they may also be used as a surrogate of infarct severity as their rise is broadly proportional to myocyte damage [536 537]. Thus it is of interest to see whether psychosocial factors and other triggers affect these markers. Other potential linking haematological and biochemical variables were also examined. The blood results which were recorded from the sample taken in the accident and emergency department were haemoglobin, white blood cell count and differential profile, platelet count and mean platelet volume (if offered by the local laboratory), serum creatinine, lipid profile, serum glucose, and serum C-reactive protein. Results were reviewed at a later date to assess peak troponin and / or creatine kinase levels. Over the course of the study one of the centres stopped processing creatine kinase assays on acute chest pain admissions and just performed

troponin assays. For statistical analyses troponin and creatine kinase measurements were split into quartiles. Upon analysis the creatine kinase results closely mirrored the troponin results and because of this and because creatine kinase measurements became used less frequently over the course of the study, only the troponin quartiles for individual trigger factors are recorded in the results tables.

7.4.3 Clinical and Electrocardiographic Findings

Clinical factors at presentation were assessed using the medical notes, the admission laboratory blood results and from review of the ECGs by a cardiologist. ECGs were specifically scrutinized for presentation as ST elevation myocardial infarction (STEMI) or non-ST elevation myocardial infarction (NSTEMI), and the pattern and distribution of the ECG changes. The discharge ECG was also analyse to look for evidence of Q or non-Q wave infarction. Admission systolic and diastolic blood pressures and the admission pulse rate were recorded from the first clinical measurement taken in the Accident and Emergency department. A proforma was designed to incorporate all of the clinical and laboratory factors of interest and was incorporated into a single document with the interview data (see appendix iii)

7.4.4 Treatment Received

This was assessed from a combination of the accident and emergency notes, the medical notes and the drug chart. Specifically we looked to see if aspirin, beta-blockers, or thrombolytic therapy had been given in the acute phase. The use of statins and ACE inhibitors was also recorded from the hospital drug charts.

7.5 THE INTERVIEW

A discussion was held with the patient to agree on a mutually suitable time to perform the interview which was convenient and would be free from interruptions. All patients conducted a structured confidential interview face to face with one of the 3 trained interviewers. No other persons apart from the patient and the interviewer were present during the time of interview to ensure confidentiality and exclude external influence on reporting of events or emotions. The interviews lasted for 30 – 60 minutes. Interviews mostly took place at the bedside with curtains drawn around the bed-space. Interviewers received instruction in interview technique prior to interviewing, and had regular feedback sessions with the study coordinators throughout the study. I personally conducted 35% of the interviews, 51% were carried out by the research sister and 24% by the post doctoral research fellow.

One of the problems with previous work in this area is that often, patient interviews have been conducted many days after the cardiac event, in some cases even after the patient has been discharged from hospital. For example Mittleman et al[115] interviewed patients an average of 4 days after their AMI but with a range extending up to 30 days. The SHEEP study [316] did not specify the time of interview. To try and ensure accurate recall of the event and the circumstances leading up to it, all patients were recruited as soon after their ACS as was feasible. We similarly attempted to interview patients as soon as possible after their ACS and attempted to do this within 4 days of their admission. At all centres, all patients were interviewed whilst in-patients on the coronary care units during their index admission, hopefully giving a greater uniformity of data collection than previous studies.

The interview data can be divided into four categories: background information, data on lifestyle and health behaviour, information concerning the circumstances surrounding ACS onset, and data relevant to triggering

7.5.1 Background Information

In addition to the information from the notes which was verified with the patient, patients were asked about their marital status (recorded as single, married, divorced, widowed, separated, living as married or other) and ethnic origin (recorded as African, Asian, Middle-Eastern, Oriental, White European, White non-European, Caribbean or other). Education was assessed by the level of qualifications attained. This was recorded as none, school certificate, GCSEs / O levels, CSEs, A levels, degree or other and subsequently classified into three: no qualifications, up to O level and A level and above for statistical analysis. The age of completion of formal education was also recorded.

Details of previous medical history were asked. In particular the presence of diabetes, hypertension and hypercholesterolaemia were sought. These were recorded as binary variables. Patients were asked about current and previous medical problems, specifically, previous myocardial infarction, previous mental illness and recent cold or influenza. Any regular medication that was being taken prior to admission was recorded. This information was later checked with the medical records and especially the use of aspirin or beta-blockers pre-admission was ascertained. Patients were also asked about family history of heart disease.

Social status was assessed by asking if their house was owned or rented, how many rooms were in the house (excluding kitchen and bathroom, whether they had the use of a

motor vehicle and by employment. Income was assessed both personally and for the entire household. The patient was asked to indicate the level of income before tax either under £10 000, between £10 000 and £20 000, between £20 000 and £30 000, between £30 000 and £40 000, or over £40 000.

To account for various facets of financial and social well-being, a "deprivation index" was constructed. This had 4 components which were scored as 0 or 1 giving a total score of 0 to 4 with 0 being the least deprived and 4 the most deprived. The components were; living in crowded conditions with over 1 person per room = 1, less than 1 person per room = 0; use of a car or van = 0, no use of a car or van = 1; living on benefits = 1, not living on benefits = 0; and living in rented accommodation = 1, living in owned accommodation = 1. For statistical analysis, this was treated as low (score = 0), medium (score = 1 or 2) and high (score = 3 or 4).

7.5.2 Lifestyle and health behaviour

Behavioural risk factors were sought such as cigarette smoking. Daily cigarette consumption (or weight of rolling tobacco) was recorded in the case of current smokers as well as length of smoking history. Ex-smokers were asked about the length of their smoking history and how long ago they had given up. Alcohol intake was assessed via units per week. Recreational pharmaceutical use of marijuana, cocaine, heroin, amphetamine or other narcotics were recorded as binary variables. Exercise was assessed by the frequency of vigorous physical activity leading to breathlessness and was assessed as the number of episodes per week over the antecedent six months. For statistical analysis, exercise was treated as none, low (one to two episodes per week), or high (greater than two episodes per week). Sexual intercourse was assessed in the same way.

7.5.3 Information Surrounding ACS Onset Circumstances of symptom onset

Patients were then questioned on the events preceding the time of ACS onset. Firstly clear recollection of the time was re-checked. Patients were asked about their experience of any premonitory symptoms in the four days beforehand and were asked about waking time on the day of ACS, normal waking time, bed-time on the night before ACS and normal bed-time. They were specifically questioned to find out if they were awake or asleep at the time of chest pain onset. Location of onset was assessed as home, work, outside, in a car, recreational activity or other. Patients were asked what they thought was happening when they experienced the pain and how long it was between symptom onset and deciding to seek medical help. They were asked if bystanders were present at the time and if the bystanders were involved in the decision making process. Bystanders were also interviewed (with the consent of the patient and the bystander) to corroborate the patient's version of events. Reasons in delays to seek help were explored. Data on delays in presenting to medical care will not be presented in this thesis but will form part of future work on health care beliefs.

7.5.4 Trigger data

Case-crossover methodology was used to allow patients to act as their own controls. The same information about potential triggers was obtained for four different periods:

a. The "hazard period": the two hours preceding symptom onset, divided into the hour immediately prior to symptoms (2nd hour) and the hour before that (1st hour temporally).

b. The "control period": the two hours corresponding to those preceding symptom onset that occurred 24-hours earlier, again divided into the 1st and 2nd hour. For example, if chest pain began at 7:00 pm on a Wednesday, the hazard period would be 5:00 – 7:00pm on the Wednesday, and the control period would be 5:00 – 7:00pm on the Tuesday.
c. The 24 hours period from the start of the control period to the start of the control period to the start of the hazard period.
d. The 6 months prior to the day of ACS onset.

The first phase of the trigger part of the interview concentrated on the hazard period two hours before the onset of chest pain. Patients were specifically asked about physical exertion in this period and this was recorded as a binary variable. Similarly, experience of exertion in the first or second hour pre ACS was recorded as binary yes / no variables. Performance of sexual activity or use of recreational drugs was recorded in the same manner. Cigarette consumption was recorded for each hour as the number of cigarettes smoked during that time. Other data recorded as binary variables were whether or not a large or fatty meal had been eaten in either of the two hours preceding ACS or whether a large amount of alcohol had been drunk, or if any unusual events had occurred.

Experience of anger during the hazard period was then asked and recorded as a binary yes / no variable, before exploring this in more depth. For either of the two hours preceding ACS onset patients were asked if they had felt mildly, moderately, very or extremely angry. To help patients they were given laminated cards with brief explanations of each level of emotion. For example, "moderately angry – body tense, clenching fists or teeth", "very angry – furious, almost out of control, slamming doors, banging tables". These scales are included as an appendix (see appendix iv). If a patient

experienced one of these levels of anger, the highest level for the hour was recorded and also the length of time it was experienced for, as well as the reason for the anger. Stress and depression were also inquired about and recorded in an identical way.

These scales were based on the scales used by Mittleman et al and by Moller et al [115 316]. The scales we used were purposefully designed to be simpler for patients to use than the 7 point scales that were used in those studies [115 316]. It was felt that the four point scale was easier to understand when conducting interviews with a largely elderly and relatively poorly educated, hospitalized population and only a minor modification to the scales used was required to achieve this. It was felt that the first two stages of anger classification that were used in these studies; "level 1 – calm", "level 2 – busy but not hassled" did not equate to a significant experience of anger and were deleted from the scale. We then merged the 2 upper levels of anger – "furious" and "enraged" into a single upper level "extremely". In a similar way to the work done in these studies, the experience of anger was treated as a binary variable in initial statistical analysis. On analyzing the data concerning anger it was noted that there was an extremely low rate or reporting the higher levels of anger. This may have been due to reporting bias, social acceptability bias or a cultural difference between our patients and those in the Onset or SHEEP studies. Consequently whereas the SHEEP and Onset studies considered exposure as having occurred at levels of anger of 5 or over on their scales, we considered positive exposure as the reporting of any feelings of anger in the time period in question.

Exactly the same data was then recorded for the control period 24 hours previously and the 24 hour period antecedent to the ACS.

Patients were then asked to describe their approximate experience of anger, stress and depression over the antecedent 6 months. Patients were asked to estimate frequency and duration (in minutes) of exposures to each of the 4 levels of anger stress and depression and also the causes thereof.

The final section of the interview looked at exposures to negative life events and stress in the 4 week and six month periods antecedent to the ACS. The presence of negative life events ("anything particularly bad, upsetting or stressful") was recorded as a binary yes / no variable. Patients were then asked whether their partner, their family, their work, or any illnesses had been a source of stress. These were recorded as yes/no binary variables. If stress had been experienced in these circumstances the, the patients were asked to rate that stress on a scale of 1-4 as done previously. They were finally asked whether they had felt any more tired than usual in the preceding 4 weeks / six months as appropriate.

At the end of the structure interview patients were asked if they had any other comments to make or questions to ask. These were recorded as felt appropriate by the interviewer.

7.6 QUESTIONNAIRES

Patients were asked to complete a set of questionnaires whilst in-patients (see appendix v). These were left with the patient on the day of the interview and were typically collected from the patient whilst still in hospital one or two days subsequently. Patients were asked to complete these unaided and were assured that all answers were confidential. In a small number of cases the patients sent the questionnaires back via the post immediately after hospital discharge if a researcher would be unable to pick up the questionnaires in person. These patients were given stamped addressed envelopes to

post the questionnaires back to the investigators once complete. The questionnaires included an adaptation of the Illness Attribution Scale, the Cardiac Denial of Impact Scale, the Acute Stress Disorder Questionnaire, the Social Network Questionnaire, the Denollet Scale for Type D personality, the Cook-Medley Hostility Scale, the Life Orientation Test, the anxiety part of the Hospital Anxiety and Depression Scale, the Maastricht Scale of Vital Exhaustion, and the Beck Depression Inventory. These questionnaire measures are not immediately relevant to the goals of this thesis, and the data are not included here. It is planned that the findings will be published elsewhere at a later date.

7.7 OTHER MEASURES

If patients were seen within 24 hours of the onset of their chest pain then permission was sought to take a further 10ml EDTA sample for future analysis. In several patients further blood sampling was not feasible, either because they had had several venepunctures previously and were unkeen to undergo further phlebotomy, or because the patients had infusions in both antecubital fossae making sampling difficult.

A proportion of patients were also asked to complete a twenty four hour salivary cortisol profile by performing eight salivette measurements over the course of the day. These were not performed if the patient's admission was complicated by factors such as heart failure or infection or other events which might cause an abnormal cortisol response. The results of these cortisol assays are not included in this thesis.

7.8 DATA STORAGE

Transcripts of interviews, consent forms, questionnaire packs and any follow up data were kept in locked cupboards with access restricted to researchers. Data was transcribed from written records onto SPSS databases. Data were anonymised and individual patients could not be identified in databases. All computerized records were kept on password protected computers with access restricted to researchers only.

7.9 FOLLOW UP

7.9.1 In Hospital Follow Up

Patients were observed whilst inpatients for any complications and the medical notes regularly examined during patient stay. If patients went on to have coronary angiography, the report was analysed to assess the extent of CAD as evidenced by number of major vessels with > 50% stenosis. This was scored from 0 to 3 vessel disease (left anterior descending, including major diagonal vessels, or circumflex artery including major obtuse marginal vessels, or right coronary artery). If the angiography films were not reported in such a way as to make this clear then the films were retrieved and reported by an independent, blinded cardiologist. Hospital notes were examined after discharge to ensure that any medical complications during admission had been noted.

7.9.2 Longer Term Follow Up

Plans were made with the patients for telephone interviews to take place in 3 and 12 months after their hospitalization. The results of these follow ups are not included in this thesis and will be hopefully published later.

7.10 STATISTICAL ANALYSES

The first stage of the analysis involved the comparison of the demographic and clinical characteristics of men and women in the sample. In these comparisons, χ^2 tests were used to analyse nonparametic, categorical variables, while parametric measures were analysed using t-tests. Several of the demographic measures were reclassified into larger groupings, since the number of patients in specific categories was small. Thus patients were allocated into 4 age groups - under 50 years old, between 50 and 60 years old, between 60 and 70 years old and over 70 years old. Because of the small number of people in the some of the sub-groups of the non-white European section of the ethnic origin section, all non-white groups were assessed together. Marital status was classified as currently married or not married, since the number of people who were divorced, never married, separated and widowed was insufficient. Education level analysed by age of leaving full-time education and by sub-dividing educational attainment into no qualifications, up to O level, and A level and above. Household income was categorised as below £20,000, between £20,000 to £40,000, and above £40, 000. Smoking status was assessed as never-smokers, ex-smokers or current smokers.

The study was not adequately powered to examine factors such as temporal associations of ACS onset so these are not reported.

The second section of Results (section 8.4) details the data concerning exposure to triggers. Information concerning exposure during the two-hour hazard period prior to ACS onset, and the two-hour control period (24 hours earlier) is presented. Case-crossover analysis was then used to calculate odds ratios for the risk of development of ACS after exposure to psychological factors. We compared exposure or unexposure to psychological factors in the 4 possible combinations during these two periods. The comparisons are expressed as odds ratios with 95% confidence intervals.

The case-crossover has been specifically developed to examine intermittent exposures and their subsequent effects on abrupt outcomes answering the question "was this event triggered by something that happened just before?"[321]. It was designed to avoid control selection bias in a study of onset of myocardial infarction because of concerns about healthy volunteer bias and healthy day bias. Healthy volunteer bias is the supposedly greater likelihood of volunteers agreeing to participate in research if they are relatively healthy. Healthy day bias is due to the fact that patients who feel more ill or stressed around the assessment period are less inclined to take part in research. Consequently the bias favours recruitment of healthier people on healthier days. Similarly patients hospitalized for other conditions would be biased by whatever triggered their hospital admission e.g. car crashes or gallstones. This methodology has now become widely used and in addition to studies of acute myocardial infarction [115 311 313 314] has been used in examinations of injuries, adverse drug events, the role of air pollution and car accidents[321]. The case-crossover study is especially amenable to conditions with an abrupt onset. Consequently patients with stuttering or insidious onset of symptoms were excluded from analysis.

One of the difficult questions faced by this kind of study is whether sleep time should be excluded from the study base. Some authors have included it [311 350] whilst others[346] have excluded it in examining physical exertion as a trigger of AMI. Investigators can assume unexposure during sleep periods or can only collect data on waking hours but this requires detailed data collection of sleeping and waking times. We felt that one cannot assume emotional unexposure during a sleeping period and consequently excluded these patients from the primary analysis.

The next stage of the analysis involved comparison of the characteristics of patients who did and did not experience triggers during the hazard period. These analyses were carried out to help identify the factors that might be associated with specific types of trigger. Four different trigger factors were analysed: physical exertion, anger, stress and depression. In each case, the comparison was made between trigger and non-trigger patients. The comparisons of parametric variables were made using t-tests, while nonparametric variables were compared with χ^2 tests. The following variables were considered as factors that might differentiate trigger and nontrigger groups: age, gender, educational attainment, deprivation, day and time of day of ACS onset, premonitory symptoms, smoking status, habitual physical activity level, use of aspirin and beta-blockers prior to admission, type of ACS (STEMI vs NSTEMI/UA), levels of CRP measured in hospital, peak troponin, number of diseased vessels, and the presence or absence of Q waves. This wide range of measures was selected since these analyses were exploratory.

When a significant difference was obtained, a logistic regression was carried out to assess the strength of association after adjustment for age and gender. The logistic regressions were intended to illustrate the strength of association after adjustment for

basic characteristics of the patients. More extensive multivariate analysis was not carried out, since the other features that might have been taken into consideration were all tested separately. The results of the logistic regressions are presented as adjusted odds ratios with 95% confidence intervals. Statistical help with analyses was obtained from Professor Steptoe and Dr D. Whitehead

7.11 MISSING DATA

There were some cases in which there were missing data. Analysis was performed for as much of the data as possible in those patients. Consequently there is variation in the total number of patients in some analyses. Particularly there is a difference in the number of patients with data missing from two hours pre ACS as some patients were still asleep at this time preventing data collection.

Chapter Eight

THE ACCENT STUDY: RESULTS AND DISCUSSION

8.1 PATIENT DEMOGRAPHICS

The mean time from admission to interview was 2.56 ± 1.6 days. 90% of interviews were completed within the target 4 days of hospital admission, and only two patients were interviewed more than a week after admission.

The study population comprised of 263 patients who were seen and interviewed over the study period (demographics seen in table 8.1). Men were on average 7.3 years younger than the women (men mean 58.5 years, women 65.8 years). The population was predominantly (83.3%) white European in its ethnic origin.

There were a highly significantly greater proportion of men who were married (70.5% compared with 41.8% of women $p < 0.001$). Females were more likely to have never married or to have been pre-deceased by their spouse. The population as a whole was relatively poorly educated with almost half of the overall population having no educational qualifications and a mean age of completion of education of 16 years old.

The majority of men (60.5%) were employed with about a third being retired, for women the pattern was the opposite with the majority reporting that they were retired (63.0%) and only one third in employment. Despite the high level of employment, mean household incomes were low with participants most frequently (43.3%) reporting

incomes of less than £20 000 per annum (this included those on pensions and benefits and included all sources of income to the household). The study population came from across the social spectrum with 44% classed as living in conditions of low deprivation and 29% living in high deprivation as rated by the previously discussed deprivation index.

11% (29 patients) of both men and women were asleep immediately prior to the onset of ACS symptoms and so they were discounted from analysis of trigger factors as discussed in Chapter 7. Trigger analysis was performed in 234 patients.

8.2 STUDY EXCLUSIONS

There were a large number of patients admitted to the recruiting centres that were labelled with diagnoses of ACS but were not suitable for inclusion in the study. It was not possible to keep accurate registry data at all sites throughout the study. These patients were audited at two of the recruiting centres, St George's and University College Hospitals NHS Trust (table 8.3). During this period 32 patients were recruited at the 2 centres to 126 patients who were excluded giving a recruitment rate of 20.3% during those 3 months.

8.3 CLINICAL DETAILS

8.3.1 Clinical and Electrocardiographic Presentation

The majority of patients (69.2%) presented with STEMI, with 11.8% presenting with ST-segment depression, 7.0 % presenting with T-wave changes, and 12.0% presenting with

non-diagnostic ECGs but having troponin T assays of > 0.1μg/l. There was a small amount of cross-over as some patients were coded as presenting with both T-wave changes and ST depression. The final ECG was evenly split between QWMI and NQWMI with a small number having bundle branch block. Clinical findings on admission are seen in table 8.4. There were no significant differences between men and women.

There was a trend towards current smokers being more likely to sustain STEMI ($p = 0.060$) and also a trend for those who had had a cold or flu within the last 2 weeks sustaining STEMI rather than NSTEMI ($p = 0.088$). STEMI patients presented with higher white blood cell counts than NSTEMI patients ($p = 0.002$) and they manifested higher peak CK and troponin measurements and were more likely to develop Q waves on their final ECG.

8.3.2 Treatment

As expected over 98% of patients received aspirin and over 80% received a beta-blocker. 83.5% of STEMI patients received thrombolytic therapy. This is likely to be due to a small number of patients who underwent primary angioplasty, a small number of initial misdiagnoses and a larger number of patients who presented out of the 12 hour window for thrombolysis.

Ultimately, patients were most likely to be treated with angioplasty. Whilst the prevalence of treatment by angioplasty was the same in men and women there was a trend towards greater prevalence of medical treatment and less CABG being performed in females (Table 8.4). There was a significant gender bias in whether patients received

coronary angiography with less women than men being investigated invasively (p = 0.010).

8.4 EXPOSURE TO TRIGGERS

The results of exposure to potential trigger factors are seen in tables 8.5-8.7. Table 8.5 shows the exposure of patients to potential trigger factors in the "hazard period" (the first and second hours before ACS onset) The "first hour" is the first chronological hour of the two hour hazard period and the "second hour" is the subsequent hour, the hour immediately pre-ACS onset. The total exposure to any putative trigger in the population was 48.3%.

As discussed in chapter 7 it is interesting to look at absolute exposures but it is important to use a control period to assess whether or not an exposure is likely to have been a triggering factor. The prevalence of exposures to potential trigger factors in the control period (the same two hour period twenty four hours previously) are shown in table 8.6. Exposure to potential triggers such as sexual activity, drugs, heavy alcohol intake, heavy meals and unusual events were too small to examine with further statistical analysis. Consequently the effects of physical activity, anger, stress and depression were analysed further.

8.5 CASE-CROSSOVER ANALYSES

Table 8.7 shows the case-crossover data for the combined 2-hour hazard period compared with the control period. It can be seen that effects were significant for physical exertion, anger, stress, anger and stress combined, any emotion, and any trigger.

What these results indicate is that there is a significantly raised likelihood of ACS onset occurring in the two hours following these exposures, in comparison with the control period. The effects for smoking, having a heavy meal and depression were not significant. The individual factors associated with triggering are discussed in more depth below.

8.6 TRIGGERING OF ACS

8.6.1 Triggering of ACS by Physical Activity

Analysis of the case-crossover data shows that there is a relative risk of 2.71 (95% confidence intervals 1.09 to 7.64) for the effect of physical activity acting as a trigger for ACS in the subsequent 2 hours (see table 8.7). It was more common to experience physical exertion in the immediate hour pre ACS (8.3%) than it was in the hour before that (3.5%). The odds ratio is significant for the hour immediately preceding ACS at 4.75 (95% confidence interval 1.58 to 19.2) but not for the hour preceding that OR = 1.33 (95% confidence interval 0.41 to 4.66, see tables 8.8 and 8.9).

Table 8.8 shows the data correlating physical exertion as a trigger factor and other clinical and demographic details. There was a strong association between exercise triggering and the absence of premonitory symptoms ($p = 0.001$). 14% of ACS in patients without premonitory symptoms were triggered by physical exertion, compared with only 1.1% of ACS preceded by symptoms. In logistic regression, the odds of sustaining an ACS in the 2 hours following physical exertion were 13.1 among patients with no premonitory symptoms compared with those who had some symptoms over the previous 4 days, after adjusting for age, gender and ethnicity.

There was no effect from hypertension, smoking, previous MI, or pre-treatment with aspirin or beta-blockade. There was a significant relationship between triggering with physical activity and subsequent troponin release. After adjusting for age and gender the odds ratio of being in the highest quartile of troponin release following exercise-induced ACS is 3.98 (95% confidence interval = 1.40 to 11.3, p = 0.009).

Patients who reported that they exercise once a week or less frequently (graded as "low") had a greatly increased risk of exertion–induced ACS compared with patients who were completely inactive or those who exercised frequently (p = 0.001). In comparison with inactive patients, the odds of triggering by physical activity for patients who were active at a low level were 7.70 (C.I. 2.42 to 24.5). By contrast, the risk for patients who were habitually highly active were not significantly elevated.

8.6.2 Triggering by Emotional Factors

The odds ratio of any emotion (anger, stress or depression) acting as a trigger for ACS was 2.71 (1.52 to 3.03). The distribution of anger, stress and depression ratings are shown in table 8.9. As can be seen the majority of people report lower rather than higher levels of negative emotions and all levels were included for analysis. 40.1% of the population were exposed to emotional stimuli in the 2 hours pre ACS. 20.4% were exposed in the hazard period only and 7.5% exposed in the control period only. 19.4% reported exposure in both periods. Unlike physical exertion, there was no difference for any of the emotional factors in the risk of ACS occurring whether emotional exposure occurred in either the first or second hour pre ACS onset. The factors associated with

triggering by any emotion are not presented in detail, since I have concentrated instead on triggering by the three emotional states separately.

8.6.3 Triggering by Anger

Anger was experienced by 17% of the population in the either or both of the 2 hours preceding ACS compared with 10.5% in the control period (see table 8.7). 13.3% were exposed in the hazard period alone and 6.7% in the control period alone. The odds ratio for anger triggering ACS was 2.00 (95% confidence interval 1.04 to 4.00).

Table 8.10 shows the data correlating anger as a trigger factor and other clinical and demographic details. There was no difference in gender, ethnicity, or marital status in experience of anger pre-ACS.

However, anger was most likely to act as a trigger on a weekday and not a weekend day ($p = 0.036$) which is a new finding, although there were no other temporal patterns. Prior aspirin or beta-blocker therapy did not affect triggering incidence by anger, nor did traditional cardiovascular risk factors such as diabetes, hypertension or hypercholesterolaemia. Whereas premonitory symptoms affected triggering by exertion, there was no effect on anger, probably because anger is less easily avoided despite the presence of symptoms.

ACS triggered by anger was more likely to be STEMI rather than NSTEMI ($p = 0.037$). Despite this effect however, anger as a trigger was not associated with measurably more severe infarction as assessed by CK, troponin, presence of Q waves, angiographic extent of coronary disease or subsequent heart failure.

8.6.4 Triggering of ACS by Stress

Exposure to stress was associated with an increased risk of ACS in the case-crossover analysis, with an odds ratio of 2.71 (95% confidence interval 1.44 to 5.42). The effect was significant for both the first and second hour prior to symptom onset. Table 8.11 shows the data correlating stress as a trigger factor and other clinical and demographic details. Unlike the position for anger, no significant associations were identified.

8.6.5 Triggering of ACS by Depressive Symptoms

A total of 20% of patients reported depressive symptoms in either or both of the two hours in the hazard period pre-ACS compared with 14.2% in the control period (see Table 8.5 an 8.6). In the case-crossover analysis, 8.8% of patients were exposed in the hazard period only and 4.0% in the control period only. The odds ratio of depressive symptoms acting as a trigger immediately pre-ACS was 2.22 (95% confidence interval 0.97 to 5.54).

Although the case-crossover effect was not significant, I still thought it of interest to analyse the factors associated with triggering by depression. Table 8.12 shows the data correlating depressive symptoms as a trigger factor and other clinical and demographic details. Patients reported that they were most likely to report depressive symptoms pre-ACS in the morning period (06.00 to 12.00) ($p = 0.020$). Patients were also more likely to experience depression preceding ACS on a weekday rather than a weekend day ($p = 0.001$).

8.7 DISCUSSION

8.7.1 General

The main findings of this study have been to confirm the role of anger and physical exertion as precipitant triggers of ACS and to identify the potential role that acute stress and depressive symptoms play in triggering. Furthermore it has extended research on triggering beyond acute MI to other forms of ACS, has identified relationships between behavioural and psychological triggers and clinical parameters, and has identified social factors which modify these psychological triggers.

The ACCENT study population was similar in demographics, risk factor profile, and clinical course to populations in other studies of trigger factors [115 246 254 309 316]and studies of unstable coronary disease despite the rigorous exclusion criteria [541-543]. Most of these studies purely dealt with AMI but the proportions of patients with STEMI/NSTEMI are similar to those studies where this has been measured and in addition there were a small percent of patients who were diagnosed as having an ACS purely on the evidence of raised troponin T. The mean age of the population (60.03 years) is lower than seen in registry data such as from studies such as the GRACE study [543]. This is probably due to the upper age limit cut-off and the exclusion of patients with significant co-morbidity which would exclude elderly rather than younger patients. The mean age is however close to the mean age of 61.3 years reported by Mittleman et al in the Onset studies[115 312]. Most studies of trigger factors have reported patient age in groups and have not reported a mean age, so comparison here is not always possible [246 254 309 316]. The population overall was poorly educated, inactive, and had many features of social deprivation.

The incidence of prior MI was low at only 9.5% compared with 29% of the Onset population although it is close to the incidence reported in the MILIS study[254]. It is likely that a number of people presenting with a second MI were excluded for reasons of age, co-morbidity, recent ACS / intervention or pulmonary oedema. It is also important to bear in mind that the history of prior MI was self-reported by the patient with no corroborating evidence. Only 20.2% of the ACCENT population took aspirin pre-admission and 15.6% took beta-blockers. This compares with 30% and 20% respectively in the Onset study; the SHEEP study didn't report aspirin use but 9.4% of that population took beta-blockers. Only 13% of the MILIS population had taken aspirin pre AMI and 21% beta-blockers. 43.0% of patients were hypertensive and 12.9% were diabetic (compared with 44% and 19% respectively in the Onset study [115], 45% and 17% in the MILIS study [254] and 31.8% and 20.2% in the SHEEP study [316]).

The men had a significantly greater body mass index than the women with a mean of 27.3 ± 4.5 versus 26.0 ± 4.7 $p < 0.001$ (see Table 8.2). This body mass index is higher than is regarded as the optimum BMI for longevity in both sexes [538]. The population was relatively inactive with 63.5% of patients doing no physical activity at all and only 16.3% doing activity twice weekly or more frequently. Approximately 42% of both sexes had had premonitory symptoms in the 4 days preceding their ACS onset. This usually took the form of episodes of milder chest discomfort and is comparable to previous reports of premonitory symptoms [254].

Over 80% of the men in the population were smoking or had previously smoked, 44.3% were current smokers. This is comparable with data from other studies of triggering [254] [316]but is higher than the national average for the U.K. or the figures for the local health authorities involved in the study[2]. This was a significantly higher proportion than was

found in the women (p = 0.006). Similarly, men were more likely to be drink alcohol and consumed more units of alcohol per week than the women.

Patients taking aspirin before their admission were more likely to present with NSTEMI rather than STEMI (p = 0.031) although no effect was seen for beta-blockers. This effect of aspirin is supported by ACS registry data and other work [286a-e] [540]. This is likely to be due to the anti-platelet effect of aspirin inhibiting intravascular coagulation after plaque rupture. The majority of patients presented with STEMI (69.2%) which was over twice as frequent as NSTEMI in both sexes although there was no difference between the sexes. This compares closely to the incidences reported in recent large studies of ACS such as the TACTICS-TIMI 18 study [542]and the GRACE registry[543]. Only a small number of patients presented with bundle branch block (3.4%). There was no significant difference in the territory of infarction.

The final ECG was equally distributed between Q and non-QWMI in men and women. The incidence of secondary heart failure and arrhythmias were low probably again due to the stringent exclusion criteria removing the most ill patients from the study, there were no significant sex differences in their incidence. The mean peak CK was higher in males than females (1407 ± 1461 versus 948 ± 1181). The wide confidence intervals just prevent this from reaching statistical significance (p = 0.053) but this difference is likely to be due in part to the size difference between the men and women. In a recent analysis of biomarker data from the TACTICS TIMI 18, OPUS-TIMI 16 and TIMI 11 studies fewer females had raised CKMB fractions or raised troponin levels at the time of ACS [544], although females were more likely to present with a raised CRP, raising the interesting question of whether there may be mechanistic differences in the pathophysiology of triggering between the two sexes.

It was surprising and worrying to find a gender bias in the referral for in-patient coronary angiography (92.0% men versus 78.4% of women p = 0.01 received angiography). There was no difference between the sexes in ECG or markers of myocyte necrosis. It may partly be due to the fact that the women were generally older than the men, but that then implies age bias. Most recent work has not identified a gender difference [545] [546]. It is beyond the scope of this thesis to discuss this further but this finding certainly merits further investigation.

The result of the audit of exclusions shows how the strict exclusion criteria severely limited the number of recruited patients. A large number of patients with an initial label of ACS were subsequently shown not in fact to have ACS on ECG or biochemical criteria and had been initially misdiagnosed (see Table 8.3). Other main reasons for exclusion were age, the presence of serious co-morbidity and the inability to speak English adequately for interview. A small number of patients declined to participate in the study. It was not possible for researchers to visit each site daily and so accurate registry data is not available for the whole study period. It is likely that there were a number of patients at each centre who were missed.

Some of the differences between the main 2 sites are visible from the audit. Both centres were audited over an intensive 3 months period where researchers attended as often as possible and followed up all admissions to discharge. UCH admitted many more patients with initial diagnoses of ACS that were subsequently disproven. CCU in UCH functions as a 10 bedded monitored ward tends to receive the majority of chest pain admissions. St. Georges CCU is a smaller more targeted facility for treatment of AMI and percutaneous intervention (PCI) patients, it also acts as a facility that receives transfers from other

hospitals for PCI and then transfers them back to their referring centre, hence the greater patients classified as recruitable but missed. St George's Hospital performs PCI on site but at UCH this is referred to a nearby hospital.

Case Crossover Analyses

It is only by looking at these comparisons that we can get an idea of the relative risks due to trigger factors. For example when looking at a frequent exposure like cigarette smoking, we see that there is an exposure to this in 35.6% of patients in the 2 hours pre-ACS perhaps initially suggesting that this may be a potent trigger factor. However it is only when one assesses the control period that an exposure in that time period of 39.0% is seen and that it is impossible to ascribe a role for smoking in the genesis of ACS as it is such a frequent exposure and most smokers smoke a cigarette at least every one to two hours. Patients reported that they were more likely to have smoked in the control periods rather than the hazard period. This may reflect a reporting bias on behalf of the patient but also may reflect a decrease in smoking in those were feeling ill or worried because of premonitory symptoms.

Exposure to Triggers

Overall there is an absolute reported exposure in 48.3% of the population to all triggers in the hazard period. This is very close to the value found in the MILIS study (48.5%) [254] and the study by Miric et al (44%) [310] and is between the values found in the SPRINT and TRIMM studies [309] [245] and so the populations are comparable in this respect.

There was a non-significant trend towards more men reporting triggers than women (40.3% versus 30.3% p = 0.33). There was no significant effect of age (although previously, younger patients have been identified as being more likely to report triggers [254 309 318]).

The exposure to physical activity pre-ACS of 11.3% falls towards the lower end of the range of published data which extends from 7.1% in the main TRIMM study [346] to 27.1% in a case series in New Zealand[345]. The ACCENT population was a relatively inactive population with little work or leisure-time physical activity which would affect the absolute value exposure to physical activity in the hazard period and thus its likelihood of acting as a trigger.

The incidence of sexual activity in the hazard period was low at 1.3%. There may be an element of underreporting responsible for this figure. However this is comparable with other data, In the Onset study, sexual activity was reported within two hours of MI by 3.0%[367]and by 1.3% in the SHEEP study[317].

The value of 40.1% exposure to any emotional trigger falls between the 18.4% found in the MILIS study [254] and the 52% found in the 24 hour antecedent period in the TRIMM study [245]. The similarity of these data with other published work suggests that the prevalence of triggers is similar in this population of ACS patients diagnosed using new criteria to the post AMI populations previously studied.

8.7.2 Physical Activity

The odds ratio for triggering of ACS by physical exertion (2.71) is comparable to other data which ranges from a relative risk of 2.1 to 5.9 in different studies [311 346 350]. It is particularly interesting that the impact of physical activity triggering was very acute, with increased odds for the hour immediately before symptom onset (4.75), but not for the hour before that (1.33, see Tables 8.8 and 8.9). It seems likely that patients who are experiencing chest pains as premonitory symptoms are likely to avoid exertion hence the lower reporting of exertion-induced triggering in patients with premonitory symptoms. Premonitory symptoms were also less likely to be associated with exertion triggered ACS in the MILIS study [254].

Clearly the risk of exertion inducing ACS in patients who do not exert themselves at all will be low but it seems as though more regular exercise has a protective effect on exertion-induced ACS. This is in-keeping with work from other studies [311 346] showing a dramatic rise in the relative risk of exertion-induced infarction in the infrequently active compared with the regularly active. This is discussed in detail in chapter 5. It has been noted before that AMI triggered by physical exertion was more likely to be associated with greater release of creatine kinase (CK)[351]. This data was confounded by the fact that CK is also released from muscle during exercise, and so unless a specific cardiac isoenzyme of CK (CKMB) is analysed then it is hard to truly know the source of the CK. Consequently it is interesting to note that exertion-induced ACS is more likely to be associated with high levels of troponin release. It may be that the cardiac demands of exertion exacerbate the myocardial damage done by acute myocardial infarction. Also it has been noted that there is increased intra-arterial thrombus and a greater chance of complete vessel occlusion in exertion-induced infarcts [351], potentially increasing

myocardial damage. Several studies have shown less advanced coronary disease in patients with exertion-induced ACS. This study has found that patients are more likely to have single vessel disease than two or three vessel disease ($p = 0.012$) a finding similar to that of Giri et al [351].

8.7.3 Anger

There was a trend ($p = 0.096$) towards anger being a trigger in younger patients. Anger was significantly more likely to be a trigger in the most deprived patients ($p = 0.021$ most deprived tertile versus least deprived tertile) suggesting an interaction between social and psychological factors. In comparison with the least deprived patients, the odds of triggering by anger were increased more than 3 times in the most deprived group, after controlling for gender, age and ethnicity. 17% of patients reported anger in the hazard period. This value encompasses the entire range from mild to severe anger. The Onset investigators only analysed their patients who reported being very angry or furious before their AMI and found a prevalence of 2.4%. In the SHEEP study the absolute incidence of intense anger in the hour preceding onset was 1.2% [316]. Neither study report however on the wider range of levels of anger experienced.

Mittleman et al have previously shown a modifying level of education on anger triggered AMI [312] but there are no data looking at other indices of social deprivation. It is therefore interesting that the most socially deprived patients had the greatest risk of anger-triggered ACS. This study did not find that educational attainment affected the incidence of anger-induced ACS. People with low job control, a concept related with low SES, have been identified as having greater anger expression [547]. This may contribute towards the increased risk of CAD or ACS in low SES groups. There was a trend ($p = 0.09$)

towards people of lower SES experiencing anger more frequently in the hazard period and it is possible that there is an interaction between social and psychological factors in determining the risk of triggering.

Another example of the interaction between psychosocial risk factors is the finding that anger is more likely to trigger ACS on a weekday compared with a weekend day. Given the young mean age of the population studied, the trend towards triggering happening in younger patients and that over 60% of them were currently working; it is possible that an interaction with work stress modulates expression of anger and the risk of anger-induced ACS.

The finding that anger leads to an increased incidence of STEMI is also interesting, and attracts conjecture about the underlying mechanisms. The increased STEMI incidence almost certainly comes from a higher incidence of total coronary arterial occlusion. This must be due either to increased obstruction to flow – greater intra-arterial clot formation or decreased flow due to arterial constriction. Anger has previously been identified as a cause of coronary vasoconstriction [512] and so this effect is very likely to play a part. Similarly, coronary arterial vasoconstriction to mental stress has been identified in laboratory studies as occurring most in those with the greatest haemodynamic reactivity to stress[508]. One can hypothesise that there is a group of the population who are at increased risk of ACS because of their physiological responses to psychological and environmental stimuli. As discussed in chapter 5, anger also has effects on haemodynamics and haemostasis, and so it is possible that more severe plaque rupture could occur due to haemodynamic stresses, and that greater clot formation could occur because of increased activation of platelets and clotting factors. Laboratory studies will be needed to test this hypothesis further.

Stress was also identified as a trigger of ACS in a proportion of patients, and there was considerable overlap between anger and stress. 69 patients reported stress in the 2 hour hazard period, compared with 39 reporting anger (table 8.5), but the number experiencing one or other was only 82, indicating that most angry patients were also stressed. Nevertheless, no specific correlates of triggering by stress were identified, suggesting that the effects anger did not generalise to related negative emotions.

8.7.4 Depressive Symptoms

As with anger, the increased likelihood of depressive symptoms triggering ACS on weekdays compared with weekend days strongly suggests an interaction with psychological stress from the working environment. In an interesting adjunct to this, depressive symptoms showed a strong effect of being most powerful in the morning between 06.00 and 12.00. As discussed in Chapter 4, the body undergoes diurnal variation in a large number of physiological systems leading to a pro-thrombotic environment favouring the onset of ACS in the morning period. Depression is well known to be more pronounced in the morning [548 549], and to have powerful biological effects, and depressive symptoms may too be more pronounced and may interact with and influence endogenous physiological functioning leading to ACS.

8.8 SOURCES OF BIAS

There are several sources of potential bias which could have influenced the presentation, selection and information gathering and interpretation in this study. It is a requisite in this study that the patients were hospitalized because of their ACS, consequently the

population may not be totally representative of the entire ACS population as there may be sources of presentation bias. There may be some patients who suffer ACS but choose to stay at home and not present to the medical services, and there will also have been a number of patients with ACS who died suddenly or before reaching medical attention. Potentially, the severest forms of ACS were not examined in this work. Similarly the strict exclusion criteria narrowed the focus of the study and so care must be taken in extrapolating the findings to all patient groups. There may also be elements of bias in referral of patients to hospital by general practitioners or in the initial treatment received in the Accident and Emergency Department. Acute emotional factors experienced by the patient may also affect their own inclination (either positively or negatively) to seek medical assistance.

We have tried as hard as possible to ensure accurate reporting of events in a strict temporally correct manner. However it is hard to guard against reverse causality with the ACS symptoms actually starting before the behavioural or psychological events. The ACS symptoms might be attributed to behavioural factors or psychological upset when this was not actually the case. Similarly there may be recall bias on the part of patients, since they may recall their psychological state at the time of chest pain onset but not remember 24 hours previously as clearly. There may also be a wish to attribute the illness of ACS to either the psychological upset or the causes thereof in an attempt to divert the responsibility for the illness away from other factors.

It is conceivable that I, as the investigator coding the admission ECG for the presence of ST elevation, having read the medical notes, may have been susceptible to bias to the presence of emotional factors based on the case history. This could have accounted for the association observed between anger and STEMI presentation. However we had not

hypothesized a specific link between the ST segment and psychological triggers before conducting the study. Similarly the coding of final ECGs for the presence of Q-waves was done retrospectively and in some cases this was done by the investigator who had performed the patient interview. Investigators were not blinded to the ECG findings when performing the interviews. Interviewers were partially masked to the study hypotheses as the intent at the start of the study was to collect data to try and establish a link rather than starting with specific hypotheses about what we might find. There was no formal comparison of the 3 interviewers who performed the patient interviews, although all received the same training and instruction in interview technique. It is possible that there were differences in interview technique and in the relationships established between individual interviewers and patients which could have affected the reporting of emotional factors.

Finally, it is also possible that alteration in mood could be a manifestation of occult or low grade illness leading to what is referred to as cytokine associated sickness behaviour [464] and may not be a primary but a secondary phenomenon.

Strengths of this Study

The strengths of this study include its strict exclusion criteria to minimize confounding from other conditions, adequate numbers to show significant effects for several psychosocial factors, a study population representative of an urban British population and comparable to other published study groups, the case-crossover design enabling the acquisition of controlled data, and the incorporation of clinical data to get a fuller picture of the effect of psychosocial triggers of ACS.

Weaknesses of this Study

Although the study numbers were adequate to show some effects, a greater number of participants would have increased the power of the study to show other significant effects. There are many potential sources of bias in the collection and recording of data as highlighted above.

8.9 CONCLUSIONS

Psychosocial and behavioural factors act as triggers of ACS. In particular, the role of anger as a trigger has been confirmed, and interactions with other social and demographic factors (age, deprivation and weekday) have been identified. The link between experience of anger and STEMI gives us further clues into the underlying pathophysiology linking the two conditions. Physical activity interacts with ethnicity and experience of premonitory symptoms in its role as an ACS trigger. The protective effect of regular exercise and the link with less severe CAD that have been observed in previous investigations have been reinforced. It is likely that depressive symptoms also have an effect on ACS triggering, an entity whose effect is modulated by occurrence in the morning and on weekdays.

Psychosocial factors and emotions affect the incidence of ACS and consequently have significant morbidity and mortality attached to them. Further laboratory studies are need to identify the harmful psychological attributes and the exact underlying physiological mechanisms of causation. Only at that time can preventative measures by implementation of either pharmacological or behavioural treatment programmes be considered.

Table 8.1 ACCENT Patient Background Demographics

	Men	Women	P value
Number	208	55	
Age (mean)	58.5	65.8	p < 0.001
< 50 years old	54 (26.0%)	4 (7.3%)	
50 - 60 years old	71 (34.1%)	14 (25.5%)	
60 - 70 years old	42 (20.2%)	14 (25.5%)	P < 0.001
> 70 years old	41 (19.7%)	23 (41.8%)	
Ethnicity : white	169 (81.3%)	48 (87.3%)	0.42
non – white	39 (18.7%)	7 (12.7%)	
Marital status: married	147 (70.7%)	23 (41.8%)	
: not married	61 (29.3%)	32 (58.2%)	0.001
Education: none	92 (43.8%)	29 (52.7%)	
: up to O level	47 (22.6%)	13 (23.6%)	0.34
: A level and over	69(33.2%)	13 (23.6%)	
Age completing education (mean years old)	16.7 (±3.4)	16.4 (±3.2)	0.45
Occupation : employed	126 (60.6%)	18 (33.3%)	
: unemployed	19 (9.1%)	2 (3.7%)	< 0.001
: retired	63 (30.3%)	34 (63.0%)	
Household income			
< £20 000	80 (40.6%)	34 (65.4%)	
£20 000 to £40 000	62 (31.5%)	16 (30.8%)	< 0.001
> £40 000	55 (27.9%)	2 (3.8%)	
Deprivation index			
Low	91 (43.8%)	23 (41.8%)	
Medium	56 (26.9%)	16 (29.1%)	0.93
High	61 (29.3%)	16 (29.1%)	

Unemployed includes those not working because of disability

Table 8.2. ACCENT Patient Lifestyle and Risk Factor Profile

	Men	Women	P value
Number	208	55	
Body mass index (BMI)	27.3 ± 4.5	26.0 ± 4.7	P< 0.001
Smoking Status : never	35 (16.8%)	21 (38.2%)	
: ex	80 (38.5 %)	36 (29.1%)	P = 0.006
: current	93 (44.7%)	18 (32.7%)	
Alcohol consumption			
Non –drinker	57 (27.4%)	38 (69.1%)	P=< 0.001
Drinker	151 (72.6%)	17 (30.9%)	
Mean units alcohol per week	12.5 ± 18.0	3.9 ± 13.1	P = 0.002
Recruitment Centre			
UCLH trust	59	14	
Southend	34	8	0.76
St. George's	115	33	
Diabetes Mellitus	28 (13.3%)	6 (10.9%)	0.64
Hypertension	84 (40.0%)	29 (52.7%)	0.095
Hypercholesterolaemia	96 (47.1%)	33 (61.1%)	0.092
Previous MI	18 (8.7%)	7 (12.7%)	0.27
Mean exercise frequency			
Inactive	130 (62.5%)	37 (67.3%)	
Low	42 (20.2%)	11 (20.0%)	
High	36 (17.3%)	7 (12.7%)	0.68
Aspirin pre-admission			
Yes	40 (19.0%)	13 (23.6%)	0.45
No	170 (81.0%)	42 (76.4%)	
Beta-blocker pre-admission			
Yes	33 (15.8%)	8 (14.5%)	1.00
No	176 (84.2%)	47 (85.5%)	

Table 8.3 Audit of screened patients excluded from the study

	UCH	St Georges
Total excluded	64	62
Not proven ACS	23	9
Comorbidity	13	13
No English	8	7
No definite onset time	6	12
Too ill / pulmonary oedema	6	9
Refused	2	2
Psychiatric problems	1	0
Alcoholic	1	0
Too old	12	7
Recent PCI	1	3
Missed	2	10
Patients recruited	10	22

Table 8.4 Clinical characteristics and Treatment on admission, men versus women

	Men	Women	P value
Admission SBP (mean ± sd)	145.1 ± 28.3	144.9 ± 27.5	0.95
Admission DBP (mean ± sd)	87.7 ± 17.8	82.3 ± 21.3	0.062
Admission pulse (mean ± sd)	77.2 ± 19.7	77.4 ± 23.0	0.94
Treated with Aspirin on admission	205 (98.6%)	53 (98.1%)	1.0
Treated with Beta-blocker on admission	178 (89.0%)	43 (79.6%)	0.11
Thrombolytic treatment on admission	123 (60.9%)	29 (53.7%)	0.35
Underwent angiography			
Yes	185 (92.0%)	40 (78.4%)	
No	16 (8.0%)	11 (21.6%)	0.010
Ultimate treatment plan			
Medical	48 (25.3%)	20 (42.6%)	
Angioplasty	109 (57.4%)	24 (51.1%)	0.024
CABG	33 (17.4%)	3 (6.4%)	

Table 8.5 **Exposure to triggers – hazard period**

Number of patients with percentage in parentheses

	1st hour of hazard period	2nd hour of hazard period	Either or both hours
Physical activity	14 (6.0%)	23 (9.8%)	27 (11.3%)
Smoking	68 (33.8%)	56 (28.1%)	72 (35.6%)
Sexual activity *	1 (0.8%)	2 (1.5%)	3 (2.6%)
Drugs	1 (0.4%)	0	1 (0.4%)
Large quantity of alcohol	0	0	0
Heavy meal	6 (2.6%)	4 (1.8%)	7 (3.1%)
Other unusual events	2 (0.9%)	3 (1.3%)	5 (2.2%)
Anger	26 (11.6%)	26 (9.8%)	38 (17.0%)
Stress	53 (23.7%)	61 (26.9%)	67 (30.0%)
Anger or stress	68 (30.0%)	64 (28.3%)	79 (35.5%)
Depression	37 (16.2%)	34 (15.2%)	43 (20.0%)
Any emotion	78 (34.2%)	74 (32.6%)	90 (40.1%)
Any trigger+	96 (40.3%)	89 (37.4%)	113 (48.3%)

* analysis limited to the sexually active
+ Physical activity, any emotion, heavy meal, unusual events

Table 8.6 **Exposure to triggers –control period**

Number of patients with percentage in parentheses

	1st hour of hazard period	2nd hour of hazard period	Either or both hours
Physical activity	8 (3.4%)	12 (5.1%)	15 (6.3%)
Smoking	65 (31.7%)	79 (38.5%)	79 (39.0%)
Sexual activity*	0 (0%)	2 (1.5%)	2 (1.5%)
Drugs	0 (0%)	0 (0%)	0 (0%)
Large quantity of alcohol	0 (0%)	0 (0%)	0 (0%)
Heavy meal	2 (0.8%)	3 (1.3%)	4 (1.5%)
Other unusual events	1 (0.4%)	2 (0.9%)	2 (0.9%)
Anger	17 (7.5%)	21 (9.3%)	23 (10.5%)
Stress	40 (17.5%)	38 (14.3%)	43 (19.2%)
Anger or stress	45 (19.7%)	43 (19.1%)	49 (21.9%)
Depression	29 (12.7%)	28 (10.6%)	32 (14.4%)
Any emotion	54(23.8%)	54 (23.8%)	61 (27.0%)
Any trigger+	63 (26.6%)	62 (26.1%)	72 (30.8%)

* analysis limited to the sexually active

+ Physical activity, any emotion, heavy meal, unusual events

Table 8.7 Case – crossover analysis of triggers over the two hour hazard period

	Unexposed – hazard Unexposed – control	Exposed – hazard Exposed – control	Unexposed – hazard Exposed – control	Exposed – hazard Unexposed – control	Odds ratio 95% C.I.
Physical activity n=234	200 (85.5%)	8 (3.4%)	7 (3.0%)	19 (8.1%)	2.71 (1.09 to 7.64)*
Smoking n=196	112 (57.1%)	67 (25.3%)	12 (6.1%)	5 (2.6%)	0.42 (0.12 to 1.27)
Heavy meal n=225	214 (95.1%)	0	4 (1.8%)	7. (3.1%)	1.75 (0.45 to 8.15)
Anger n=225	172 (76.4%)	8 (3.6%)	15 (6.7%)	30 (13.3%)	2.0 (1.04 to 4.00)*
Stress n=226	145 (64.2%)	29 (12.8%)	14 (6.2%)	38 (18.8%)	2.71 (1.44 to 5.42)*
Anger or stress n=225	127 (56.4%)	30 (13.3%)	19 (8.4%)	49 (21.8%)	2.58 (1.49 to 4.64)*
Depression n=226	174 (77.0%)	23 (10.2%)	9 (4.0%)	20 (8.8%)	2.22 (0.97 to 5.54)
Any emotion n=227	120 (52.9%)	44 (19.4%)	17 (7.5%)	46 (20.4%)	2.71 (1.52 to 5.03)*
Any trigger[+] n=234	100 (42.7%)	51 (21.8%)	21 (9.0%)	62 (26.5%)	2.95 (1.77 to 5.10)*

[+] Physical activity, any emotion, heavy meal, unusual events

* Significant effects with CI not crossing 1.

n = number of patients included for data analysis with complete information

Table 8.8 Triggering by physical activity: Comparison of trigger and no exposure groups

Number of patients with percentage in parentheses

		Physical activity exposure in hazard period	No exposure	P
Gender:	**Men**	18 (10.4%)	155 (89.6%)	0.13
	Women	1 (2.2%)	45 (97.8%)	
Age:	**< 50 years**	6 (12.2%)	43 (87.8%)	0.45
	50-60 years	4 (5.8%)	65 (94.2%)	
	60-70 years	6 (14.6%)	35 (85.4%)	
	>70 years	3 (5.2%)	5 (94.8%)	
Education:				
No qualifications		6 (5.8%)	98 (94.2%)	
Up to primary		6 (12.0%)	44 (88.0%)	0.22
Secondary or higher		7 (10.8%)	58 (89.2%)	
Deprivation Index				
Low		11 (12.0%)	81 (88.0%)	
Medium		4 (6.3%)	59 (93.7%)	0.33
High		4 (6.2%)	61 (93.8%)	
Time :				
< 6:00 am		0	36 (100%)	
6:00 – 12:00		5 (6.8%)	68 (93.2%)	0.010
12:00 – 18:00		11 (16.7%)	55 (83.3%)	
>18:00		3 (6.8%)	41 (93.2%)	
ACS within 3 hours of waking				
	Yes	0	25 (100%)	0.028
	No	19 (9.9%)	173 (90.1%)	
Symptoms in previous 4 days				
	Yes	1 (1.1%)	89 (98.9%)	.001
	No	18 (14.0%)	111 (86.0%)	
Smoking Status				
	Non Smoker	10 (8.0%)	115 (92.0%)	0.81
	Smoker	9 (9.5%)	86 (90.5%)	
Regular Physical Exertion				
	None	5 (3.6%)	135 (96.4%)	
	Low	10 (22.2%)	36 (78.3%)	0.001
	High	3 (9.4%)	29 (90.6%)	
Aspirin pre-admission				
Yes		3 (6.8%)	41 (93.2%)	0.77
No		16 (9.1%)	160 (90.9%)	

	Physical activity exposure in hazard period	No exposure	P
Beta-blocker pre-admission			
Yes	2 (5.9%)	32 (94.1%)	0.74
No	17 (9.2%)	168 (90.8%)	
ACS type			
STEMI	15 (10.0%)	135 (90.0%)	0.29
NSTEMI/UA	3 (4.5%)	64 (96.5%)	
Troponin quartiles			
1 (lowest)	3 (5.9%)	48 (94.1%)	
2	3 (6.4%)	44 (93.8%)	0.034
3	2 (4.5%)	42 (95.5%)	
4 (highest)	9 (20.0%)	36 (80.0%)	
Q / non Q wave infarction			
Q wave	11 (11.6%)	84 (88.4%)	0.20
Non Q wave	6 (6.0%)	94 (94.0%)	
Number vessels diseased			
1	9 (11.8%)	67 (88.2%)	
2	0 (0%)	45 (100%)	0.012
3	3 (6.7%)	42 (93.3%)	

Table 8.9 Distribution of Anger, Stress and Depression Ratings

	First Hour of hazard period	Second Hour of hazard period
Anger Level 0	201 (88.5%)	199 (75.1%)
Anger Level 1	12 (4.5%)	18 (6.8%)
Anger Level 2	6 (2.3%)	3 (1.3%)
Anger Level 3	7 (2.6%)	5 (2.2%)
Anger Level 4	1 (0.4%)	0
Stress Level 0	166 (62.6%)	171 (64.5%)
Stress Level 1	20 (7.5%)	24 (9.1%)
Stress Level 2	30 (11.3%)	22 (8.3%)
Stress Level 3	9 (3.4%)	6 (2.3%)
Stress Level 4	2 (0.8%)	1 (0.4%)
Depression Level 0	191 (83.8%)	190 (84.8%)
Depression Level 1	21 (7.9%)	17 (6.4%)
Depression Level 2	11 (4.2%)	12 (4.5%)
Depression Level 3	3 (1.1%)	2 (0.8%)
Depression Level 4	2 (0.8%)	3 (1.1%)

Table 8.10 Triggering by anger: Comparison of trigger and no exposure groups

Number of patients with percentage in parentheses

		Anger exposure in hazard period	No exposure	P
Gender:	**Men**	24 (14.9%)	137 (85.1%)	1.00
	Women	6 (14.6%)	35 (85.4%)	
Age:	**< 50 years**	10 (21.7%)	36 (78.3%)	0.096
	50-60 years	9 (14.5%)	53 (85.5%)	
	60-70 years	5 (12.5%)	35 (87.5%)	
	>70 years	5 (9.6%)	47 (90.4%)	
Education:				
No qualifications		14 (15.1%)	79 (84.9%)	0.92
Up to primary		6 (13.0%)	40 (87.0%)	
Secondary or higher		10 (15.9%)	53 (84.1%)	
Deprivation Index				
	low	6 (7.1%)	78 (92.9%)	0.021
	medium	10 (17.9%)	46 (82.1%)	
	high	14 (22.6%)	48 (77.4%)	
Day				
	Weekday	25 (18.9%)	107 (81.1%)	0.036
	Weekend day	5 (7.2%)	64 (92.8%)	
Time :	**< 6:00 am**	4 (14.8%)	23 (85.2%)	0.69
	6:00 – 12:00	10 (13.9%)	62 (86.1%)	
	12:00 – 18:00	8 (12.3%)	57 (87.7%)	
	>18:00	8 (21.1%)	30 (78.9%)	
ACS onset within 3 hours of waking				
Yes		2 (9.1%)	20 (90.9%)	0.75
No		27 (15.2%)	151 (84.8%)	
Symptoms in previous 4 days				
	Yes	10 (12.7%)	69 (87.3%)	0.55
	No	20 (16.3%)	103 (83.7%)	
Aspirin pre-admission:	**Yes**	6 (14.0%)	37 (86.0%)	1.00
	No	24 (15.0%)	136 (85.0%)	
Beta-blocker pre-admission				
	Yes	4 (12.9%)	27 (87.1%)	1.00
	No	26 (15.2%)	145 (84.8%)	

	Anger exposure in hazard period	No exposure	P
ACS type			
STEMI	25 (18.8%)	108 (81.2%)	
NSTEMI/UA	5 (7.5%)	62 (92.5%)	0.04
CRP	12.17 ± 14.87	12.83 ± 23.07	0.90
Troponin quartiles			
1 (lowest)	8 (17.4%)	38 (82.6%)	
2	5 (10.6%)	42 (89.4%)	
3	5 (12.8%)	34 (87.2%)	0.72
4 (highest)	7 (17.9%)	32 (82.1%)	
Q / non Q wave infarction			
Q wave	10 (12.3%)	71 (87.7%)	0.40
Non Q wave	16 (17.0%)	78 (83.0%)	

Table 8.11 Triggering by stress: Comparison of trigger and no exposure groups
Number of patients with percentage in parentheses

		Stress exposure in hazard period	No exposure	P
Gender:	**Men**	30 (21.0%)	113 (79.0%)	
	Women	8 (19.5%)	33 (80.5%)	1.00
Age:	**< 50 years**	11 (26.8%)	30 (73.2%)	
	50-60 years	13 (24.5%)	40 (75.5%)	
	60-70 years	8 (20.0%)	32 (80.0%)	0.31
	>70 years	6 (12.5%)	42 (87.5%)	
Education:				
	No qualifications	20 (23.0%)	67 (77.0%)	
	Up to primary	7 (16.3%)	36 (83.7%)	0.67
	Secondary or higher	11 (20.4%)	43 (79.6%)	
Deprivation Index				
	Low	12 (15.8%)	64 (84.2%)	
	Medium	15 (27.8%)	39 (72.2%)	0.26
	High	11 (20.4%)	43 (79.6%)	
Day				
	Weekday	28 (23.7%)	90 (76.3%)	
	Weekend day	10 (15.4%)	55 (84.6%)	0.25
Time :				
< 6:00 am		2 (7.7%)	24 (92.3%)	
6:00 – 12:00		12 (18.8%)	52 (81.3%)	
12:00 – 18:00		16 (27.6%)	42 (72.4%)	0.17
>18:00		8 (22.2%)	28 (77.8%)	
Symptoms in previous 4 days				
	Yes	10 (14.1%)	61 (85.9%)	0.094
	No	28 (24.8%)	85 (75.2%)	
Aspirin pre-admission				
	Yes	8 (21.6%)	29 (78.4%)	
	No	30 (20.4%)	117 (79.6%)	0.82
Beta-blocker pre-admission				
	Yes	8 (28.6%)	20 (71.4%)	0.31
	No	30 (19.4%)	125 (80.6%)	
ACS type				
	STEMI	28 (23.1%)	93 (76.9%)	0.34
	NSTEMI/UA	10 (16.4%)	51 (83.6%)	

Table 8.12 Triggering by depression: Comparison of trigger and no exposure groups

Number of patients with percentage in parentheses

		Depression exposure in hazard period	No exposure	P
Gender:	**Men**	19 (11.9%)	140 (88.1%)	
	Women	1 (2.9%)	34 (97.1%)	0.13
Age:	**< 50 years**	7 (15.6%)	38 (84.4%)	
	50-60 years	5 (8.5%)	54 (91.5%)	
	60-70 years	5 (12.8%)	34 (87.2%)	0.43
	>70 years	3 (6.1%)	46 (93.9%)	
Education:				
No qualifications		11 (12.8%)	75 (87.2%)	
Up to primary		4 (8.9%)	41 (91.1%)	
Secondary or higher		5 (7.9%)	58 (92.1%)	0.59
Deprivation Index				
	Low	7 (8.1%)	79 (91.9%)	
	Medium	8 (14.3%)	48 (85.7%)	
	High	5 (9.6%)	47 (90.4%)	0.51
Day:	**Weekday**	20 (15.7%)	107 (84.3%)	
	Weekend day	0 (0%)	66 (100%)	< 0.001
Time :	**< 6:00 am**	0 (0%)	26 (100%)	
	6:00 – 12:00	12 (17.4%)	57 (82.6%)	
	12:00 – 18:00	6 (9.4%)	58 (90.6%)	
	>18:00	2 (5.7%)	33 (94.3%)	0.02
Symptoms in previous 4 days				
	Yes	5 (6.6%)	71 (93.4%)	
	No	15 (12.6%)	104 (87.4%)	0.22
Mean exercise frequency				
	Inactive	12 (10.2%)	106 (89.8%)	
	Low	4 (10.3%)	35 (89.7%)	
	High	4 (10.8%)	33 (89.2%)	0.99
Aspirin pre-admission	**Yes**	4 (10.3%)	35 (89.7%)	
	No	16 (10.3%)	140 (89.7%)	1.00
Beta-blocker pre-admission				
	Yes	4 (14.8%)	23 (85.2%)	
	No	16 (9.6%)	151 (90.4%)	0.49

	Depression exposure in hazard period	No exposure	P
ACS type			
STEMI	14 (10.6%)	118 (89.4%)	0.79
NSTEMI/UA	5 (8.3%)	55 (91.7%)	
CRP	8.70 ± 8.15	19.6 ± 58.15	0.43
Troponin quartiles			
1 (lowest)	6 (15.0%)	34 (85.0%)	
2	6 (13.3%)	39 (86.7%)	
3	3 (7.7%)	36 (92.3%)	0.40
4 (highest)	2 (5.1%)	37 (94.9%)	
Q / non Q wave infarction			
Q wave	7 (9.0%)	71 (91.0%)	1.00
Non Q wave	9 (10.2%)	79 (89.8%)	
Number vessels diseased			
1	10 (14.1%)	61 (85.9%)	
2	3 (7.7%)	36 (92.3%)	0.58
3	4 (10.5%)	34 (89.5%)	

Chapter Nine

LABORATORY INVESTIGATION OF THE PLATELET AND HAEMODYNAMIC REACTIVITY TO MENTAL STRESS IN PATIENTS WITH CORONARY ARTERY DISEASE

9.1 INTRODUCTION

9.1.1 Background

One of the proposed mechanisms underlying both the long-term development of coronary artery disease (CAD), and the triggering of acute coronary syndromes (ACS) is heightened physiological reactivity to mental stress.

As outlined in Chapters 3, 5 and 6 several processes may display abnormal reactivity and be relevant in linking psychosocial factors with atherogenesis, plaque rupture and subsequent ACS. Two processes may be particularly relevant: cardiovascular reactivity and the activation and local aggregation of platelets. The vast majority of work has only considered the haemodynamic responses to mental stress without considering the reactivity of other physiological systems. This laboratory study was designed to examine the psychophysiological response to mental stress in patients with coronary artery disease and age-matched controls, to see if any differences existed between the two groups, and to consider if these differences could be responsible for part of the link between psychological stress and acute and chronic CAD. The study was carried out while data collection was in progress for the Accent study described in the previous

chapter, and was intended to develop psychophysiological methods that might later be applied to a sub-sample of Accent patients. We explored such issues as the feasibility of laboratory stress testing lasting more than two hours with cardiac patients, the acceptability of withdrawal from chronic medications prior to testing, and the nature of differences in haemodynamic, inflammatory and platelet responses stress between CAD patients and controls. The results of this study have recently been published [550].

Debate continues as to whether cardiovascular reactivity is a primary causative phenomenon, possibly promoting atherosclerosis via episodic hypertension and the direct and indirect atherosclerotic effects of catecholamines, or if it is simply a reflection and marker of existing vascular pathology and endothelial dysfunction. Other possible mechanisms proposed for cardiovascular reactivity being a causal factor in CAD include sympathetically driven lipid mobilization and platelet aggregation [359]and endothelial injury caused by pressor-induced blood flow disruption [551]. Definitive proof of cardiovascular reactivity as a causative factor rather than an association remains elusive and there is currently no convincing work to show that cardiovascular reactivity and atherosclerotic vascular disease are not two aspects of the same disease.

Animal evidence has supported the link between increased cardiovascular reactivity and development of atherosclerosis [545 546]. More recently there has been evidence to suggest an influence of cardiovascular reactivity on atherosclerotic disease in humans as assessed by ultrasound examination of carotid artery atherosclerosis, a surrogate of more widespread vascular disease [552]. Cardiovascular reactivity, and in particular changes in pulse pressure, predicted severity of carotid atherosclerosis 2.3 years after mental stress testing [552]. More importantly, cardiovascular reactivity is predictive of clinical cardiovascular events, with the most reactive patients being at highest risk [553].

Cardiovascular reactivity to mental stress also affects severity of mental stress induced myocardial ischaemia [502]. The majority of work on cardiovascular reactivity has been done in healthy volunteers, although there is an increasing literature in patients with CAD[554]. Although some authors have found that patients with CAD have greater blood pressure responses to stressful tasks than healthy controls [555-557], others have reported no differences [497 509 525], or heightened pressor responses only in patients who show severe ischemic changes [502]. Several factors may account for these inconsistencies. Some studies have assessed cardiovascular reactivity during inherently stressful procedures such as coronary angiography or radionuclide ventriculography [484 497 525]that may themselves affect the magnitude and duration of responses. Few other studies have attempted to look at any other physiological systems apart from haemodynamic stress responses.

It may not just be the absolute changes in haemodynamic parameters which are important. For example, the recovery time i.e. length of time that blood pressure remains elevated after mental stress may also be important. Theoretically, a longer stimulus could be more injurious and pro-atherogenic than a shorter one and has been associated with cardiovascular prognosis [558]. This recovery time has been shown to be prolonged in persons of low socio-economic status (SES) compared with higher SES controls [178].

9.1.2 Methodological issues

Despite the evidence that increased cardiovascular reactivity may be linked to CAD, care is needed in the interpretation of this as reactivity is also associated with several risk factors for CAD. There is most evidence concerning a link between cardiovascular reactivity to mental stress and future development of hypertension [559 560]. In a sample of

paediatric patients (aged between 8 to 10), cardiovascular reactivity predicted future rises in blood pressure, showing its relevance even at an early age and potentially lending support to an argument of causation [561]. There may also be an important interaction of genetic and environmental factors. Light et al found that increased cardiovascular reactivity was only predictive of future blood pressure status in persons with a positive family history of hypertension who experienced high degrees of life stress [560]. Besides hypertension, excessive cardiovascular reactivity is associated with other established CAD risk factors such as hyperlipidaemia and raised blood sugar [562]. Cholesterol lowering therapy with pravastatin improves excessive reactivity, suggesting an endothelial effect [562]. Smoking also causes an increased reactivity to mental stress [563].

Many studies have examined cardiovascular reactivity to stress but few have looked at clinical, psychological or social correlates in patients with heart disease. Personality traits such as the type A personality construct and hostility which have been linked to CAD in some studies have also been found within CAD patients to be linked to larger haemodynamic stress responses [556 557]. Similarly anger, depressive symptoms and coping methods have also been associated with exaggerated blood pressure responses to stress [148 150 564]. Cardiac and vascular reactivity increase with increasing age and with the presence of hypertension [565]. Cardiovascular reactivity may also act in concert with other social factors to increase vascular risk, for example, potentiation of the effect of low socio-economic status on carotid atherosclerosis[566]. Other psychosocial factors linked to CAD such as emotional support, work stress and experience of stressful events have also been linked to reactivity [149 567]. Consequently, great care is needed to try and minimize these as confounding factors when studying cardiovascular reactivity in relation to CAD, by controlling statistically for age, hypertension, smoking, hypercholesterolaemia, diabetes, and social and psychological factors.

In the investigation of cardiovascular reactivity, most investigators have measured blood pressure with conventional sphygmomanometry, taking readings every 2 -3 minutes. Such measures estimate blood pressure reactivity on the basis of less than 1% of data, so may not accurately reflect the profile of responses [568]. The medication status of CAD patients has been variable and not always statistically controlled [438]. In the present study, CAD patients were removed from all medications except aspirin prior to laboratory testing, and statistical adjustments were also made for previous medication status.

Assessment of cardiac output and peripheral vascular resistance responses may also be illuminating. Sundin et al [557] showed that CAD patients exhibited greater total peripheral resistance responses to stress in comparison with controls, with no post-stress return to baseline. In a study involving mental arithmetic and anger recall, Jain et al [484]reported greater increases in vascular resistance and smaller rises in cardiac output in CAD patients compared with controls, so that the pattern of haemodynamic responses differed even though the resultant blood pressure reactions were similar.

9.1.3 Stress, platelet activation, and CAD

Platelet activation is one of the fundamental factors in the pathogenesis of acute coronary syndromes [462], and may be an important mediator of psychosocial influences on CAD [569]. Studies of acute mental stress have measured platelet function with filtragometry, adenosine diphosphate (ADP) and collagen-stimulated platelet aggregation, and assays of the α-granule proteins platelet factor-4 and β-thromboglobulin [436 457 570 571]. Data relating platelet activation with mental stress in CAD patients and controls have been conflicting. Malkoff found an increase in platelet activation in healthy volunteers under

mental stress[571] whereas Wallen et al [359]found reduced platelet aggregability times and increases in platelet factor 4 and β-thromboglobulin in angina patients but not controls in response to mental stress. Markovitz et al however[436] reported a greater mental stress-induced rise in β-thromboglobulin in healthy controls than in post-MI patients, while Grignani et al [458] demonstrated greater ADP and collagen-stimulated platelet activation in response to mental stress in CAD patients versus controls.

There are few data in these studies relating changes in platelet function to other physiological parameters. Two studies have shown a correlation between norepinephrine and platelet activation, the data regarding epinephrine is unclear with Markovitz et al finding no relation but Patterson et al finding an inverse relationship [436 457]. There are also few data regarding modifying psychosocial factors of platelet activation, but Markovitz et al found that increased potential for hostility was associated with increased platelet reactivity to mental stress [436] and Wenneberg et al found that anger expression was associated with increased stress-induced [174] platelet aggregation.

Techniques for assessing platelet activation have progressed substantially over recent years, and measures of platelet-leukocyte aggregates (PLAs) based on whole blood flow cytometry have become the method of choice [572 573]. The method is based on the observation that activated platelets bind to larger blood cells, notably monocytes, lymphocytes and neutrophils. The proportion of leukocyte-platelet aggregates is therefore an *in vivo* indicator of platelet activation. This technique allows platelets to be assessed directly in their physiological milieu with minimal manipulation, preventing artefactual *in vitro* activation [574]. This technique was therefore used to compare mental stress-induced platelet activation in CAD patients compared with healthy controls.

9.1.4. Stress and acute changes in C-reactive protein

Acute mental stress causes an inflammatory response. The role of CRP in CAD and the inflammatory effects of mental stress have been discussed in chapters 2 and 5. There are no data documenting the effects of mental stress on CRP levels in CAD patients compared with healthy controls. CRP is predictive of cardiovascular risk and is synthesized in the liver in response to cytokine stimulation. CRP has also been suspected of having pro-atherogenic properties by mediating LDL uptake by macrophages [575], stimulating pro-inflammatory cytokine release [576], and promoting endothelial adhesion molecule expression [577]. Its levels are predictive of prognosis not only in the setting of unstable coronary syndromes but also of future events in apparently healthy populations [158] [159]. In addition to measures of haemodynamic and platelet reactivity, we also examined the effect of mental stress on CRP in these groups of patients. In a previous study from Professor Steptoe's laboratory, plasma CRP levels were not found to change in blood samples taken up to 45 minutes post-stress. In the present study, the hypothesis was tested that CRP concentration might increase more slowly, so be apparent in samples taken 120 minutes post-stress.

To further look at how psychosocial factors and physiology may interact to produce ACS, it is necessary to take an experimental approach and examine physiological responses to standardized laboratory mental stressors under controlled conditions. It would be impossible to focus on all of the mechanisms discussed in the preceding chapters and this experiment focused on three of the likely most important mechanisms; the pattern of haemodynamic responses and changes in platelet activation and markers of inflammation. The blood pressure, heart rate, cardiac output and peripheral resistance responses of CAD patients and age-matched healthy controls were compared using

continuous non-invasive measures. The association between individual subjective appraisal of the stress tasks and biological responses was also assessed. CAD patients were withdrawn from all cardiac medications except for aspirin, and their medication history was used as a covariate in the analyses. Cardiovascular monitoring continued for two hours post-stress, so that recovery patterns could be assessed. Two tasks were utilized to elicit stress responses, and physiological responses across tasks were aggregated, since the focus of the study was on group differences rather than between-task response profiles [578].

9.1.5 Hypotheses

The main hypothesis being tested in this study was that in comparison with healthy age-matched controls, patients with documented CAD would show disturbed cardiovascular, platelet and inflammatory responses to acute stress. Disturbed responses were defined as either heightened stress-induced reactions, or delayed post-stress recovery and return to baseline levels in the various physiological indicators tested.

Because of the small scale of this study, we decided to conduct it only with male patients, since gender differences might add a source of variance that could obscure the CAD / Control group comparison. We also decided to eliminate a second source of variance, and only study nonsmokers, since smoking has pronounced effects on many of the indicators tested, particularly platelet function and CRP. This was not completely successful, since although none of the healthy controls were smokers, we were obliged to include two smokers in the CAD group.

9.2 METHODS

9.2.1 Participants

Data were collected from 17 male CAD patients and 22 male healthy controls. All participants were white, nonsmokers and normotensive. CAD patients were recruited from the database of patients with stable angina and documented coronary artery atherosclerosis who had undergone percutaneous coronary angiography or coronary intervention in the University College London NHS Trust within the preceding 2 years. Medical notes were examined and the patients interviewed before testing to explain the procedure and ensure they fulfilled entry criteria. Patients were excluded from recruitment if they were aged below 30 or above 65, had poor left ventricular function, unstable or rapidly worsening symptoms, history of malignant arrhythmias, significant co-morbid conditions, had other major past medical problems which could affect either haemodynamic, platelet or immune responses, were not able fluent in English or able to understand the procedure. We aimed to recruit as many participants as possible, but only 17 suitable subjects consented to take part and so formed the study group. The actual age range was 44-59 years, and all patients were chronically medicated, with 15 taking aspirin, 15 statins, and 12 having β-blocker medication for cardioprotection. The healthy controls were part of a larger sample of 37 men recruited from London-based Departments of the British civil service for a study of the effects of mental stress on platelet function. They self-certified that they were free of any past or present medical problems and took no regular medications (including aspirin or statins). They were not screened for occult CAD with any test of reversible myocardial ischemia, and all were normocholesterolaemic. Results from the larger sample have been published elsewhere [579]. The participants in that study were aged 30 – 60 years, and for the present

comparison, we included the 22 individuals who were aged 44 and over, and therefore matched the CAD sample in age distribution.

The healthy controls participated in the study before the CAD patients, but the protocols used were identical. Participants in both groups were volunteers who had replied to an invitation to help in research (see appendix vi), and all were given identical information about the study and its purposes (see patient information sheet, appendix vii). There was no financial incentive to participate in either group. The study was approved by the UCL/UCLH Medical Research Ethics Committee.

9.2.2 Measures and behavioural tasks

Blood pressure and heart rate were monitored continuously from the finger using a Portapres-2 [580]. Cardiac output and stroke volume were determined from the Portapres using the aortic flow waveform method developed by Wesseling and coworkers [581], and utilized in Modelflow™ 2.1 software (TNO, Amsterdam, NL). Stroke volume is calculated from the systolic area – the area under the arterial pressure wave between the onset of the blood pressure rise and the dichrotic notch – on a beat by beat basis corrected by a calibration factor that relates to aortic compliance. Total peripheral resistance was predicted from mean pressure and computed aortic flow. Good agreement has been obtained between Modelflow™ computations from intra-arterial and finger blood pressure measures, and between finger-based measures and thermodilution [582]. Cardiac output was converted to cardiac index by dividing by body surface area. Weight, height and waist and hip circumference were measured with standard methods, and body fat was assessed using a Bodystat® 1500 bioelectrical impedance body composition analysis device (Bodystat Ltd, Douglas, Isle of Man).

Information concerning employment, marital status, smoking and alcohol consumption was collected by questionnaire. Physical activity was measured as the number of days in the past week on which participants had been moderately or vigorously active. Socioeconomic status was assessed with two measures. First, participants provided information about their annual income. In the analysis, the sample was divided according to whether annual incomes were above or below £35,000 (US$ 56,000). Second, participants completed the social "ladder". They were shown a drawing of a ladder with 10 rungs, representing where people stand in society [583]. They were told that at the top of the ladder are the people who are best off – those who have the most money, most education, and best jobs. At the bottom are the people who are the worst off, have the least money, least education and the worst jobs or no job. They were asked to place themselves on the rung on which they felt that they stood.

Depression was assessed using the depression subscale from the Hospital Anxiety and Depression (HAD) scale [584]. This measure is widely used for assessing medical patients [585], and consists of 7 items, each of which is rated on a 4-point scale, so total scores could range from 0 – 21. Higher scores reflect greater depression, and a score of 11 or more is suggestive of moderate clinical depression. Sleep problems were assessed with the scale developed by Jenkins et al [586]. This consists of four items, asking respondents how often in the past month they had woken up several times in the night, had trouble staying asleep, etc. There were six response options, ranging from 0 = *not at all* to 5 = *22-31 days*. The total was computed, so scores could range from 0 – 20.

Psychological stress was induced by two behavioural tasks previously used in this laboratory [587]. The first was a computerized colour-word interference task developed at

the University of Pittsburgh involving the consecutive presentation of target colour words (e.g. green) printed in another colour. At the bottom of the computer screen were names of four colours printed in incongruent colours, and the task was to press a computer key that corresponded to the position at the bottom of the screen of the name of the colour in which the target word was printed. The rate of presentation was adjusted to ensure sustained demands. The second task was mirror tracing, involving the tracing of a star which could only be seen in mirror image. Participants were told that the average person completed five circuits of the star in the time available, and were asked to give accuracy priority over speed.

9.2.3 Measures of platelet function

Blood for the assessment of PLAs was drawn with minimal haemostasis, using 21-gauge Butterfly® needles into Vacutainer® tubes containing sodium citrate as anticoagulant. Whole blood samples (10µl) were incubated for 20 min with 90µl Hepes buffered saline containing 10µl each of leukocyte- and platelet-specific antibodies, respectively, 6.25µg/ml fluorescein isothiocyanate-conjugated mouse anti-human CD45 monoclonal antibody (H130, BD PharMingen, Oxford) and 12.5µg/ml R-Phycoerythrin-conjugated mouse anti-human CD42a monoclonal antibody (ALMA.16, BD PharMingen). Samples were fixed with 700µl 0.5% formaldehyde solution diluted from 37% formalin solution (Sigma) after incubation. Within three hours the samples were analyzed using a Becton Dickinson FACScan Flow Cytometer and Cellquest software. The instrument was set up to acquire 10,000 CD45 positive events. Results are expressed as the percentages of leukocyte bound to platelets [574]. As detailed previously, control experiments were also carried out to assess non-specific binding [579]. The same methods of sample preparation were used, but a control antibody (R-PE)-conjugated mouse IgG1, kappa isotope was

substituted for (RPE) CD42a. The proportion of non-specific binding averaged <0.6%, and adjusting levels of PLAs for this non-specific effect did not alter the pattern of results. The platelet assays were carried out by Kesson Magid, a research assistant in Professor Steptoe's group.

9.2.4 CRP assessment

CRP was assessed at baseline and 2 hours. Blood was taken in the same sampling as for platelet function assessment and was drawn into a 10ml Vacutainer ™ tube containing EDTA as anticoagulant. Within 10 minutes of sampling, the samples were centrifuged at 1.5G for 10 minutes at room temperature. Plasma was aspirated, aliquoted, and immediately frozen at -80°C until analysed. All samples were defrosted and analysed at the same time. Plasma concentrations of CRP were determined by a commercially available high-sensitivity solid phase enzyme linked immunosorbent assay and standards (Biocheck, Burlingame, CA, USA). These assays were also carried out by Kesson Magid.

9.2.5 Procedure

CAD patients were withdrawn from all medications except aspirin for a minimum 72 hours prior to testing. Healthy controls were asked not to take aspirin for 10 days prior to testing, but to use paracetamol if they required pain medication. All sessions were carried out in the morning beginning at 9.15 am. Participants were instructed not to have drunk tea, coffee, or caffeinated beverages on the morning of the experiment, not to eat a high fat or high protein breakfast, and not to have consumed alcohol or exercised on the evening before or the day of testing (see session instructions, appendix viii). The

laboratory protocol is included as appendix ix. All participants were given the opportunity to ask questions and received informed consent. Participants were asked to sign a consent form (appendix x).

At the beginning of the session, anthropometric measures (height, weight and waist/hip ratio) were taken, a venous cannula was inserted, and the participant rested for 30 min. Blood pressure and heart rate were recorded for the last five minutes of the rest period using the Portapres, after which two readings were obtained manually with an electronic sphygmomanometer, and the baseline blood sample was drawn. The participant rated feelings of stress on a 7-point scale from 1 = *low* to 7 = *high*. The two tasks were then administered each for five minutes in fixed order beginning with the colour-word interference task. Blood pressure and heart rate were recorded continuously during tasks. At the end of each task, the participant rated task difficulty, involvement, controllability and feelings of stress on 7-point scales from 1 = *low* to 7 = *high*. A second blood sample was drawn immediately after the second task. The participant then rested quietly for the remainder of the experimental session. Five minute recordings of blood pressure and heart rate were made 25 – 30 min, 70 – 75 min and 115-120 min post-stress, and further blood samples were drawn 30 min and 75 min post-stress.

9.2.6 Ethical considerations and drug withdrawal

Patients were withdrawn from all cardioactive medication for a minimum of 72 hours prior to the laboratory study. Full discussions of the risks of medication cessation as well as the pharmacological rationale are presented in Chapter 10 with the ethical considerations. At the time ethics committee submission for this study, the committee felt that it was not ethical to withdraw patients from aspirin – a decision which was

reconsidered at the time of application for ethical approval for the study described in Chapter 10, therefore aspirin was continued in CAD patients for this study. The implications of this for the results are considered in the discussions section of this chapter.

9.2.7 Statistical analysis

The two groups were compared on anthropometric and background characteristics using analysis of variance and χ^2 tests as appropriate. The blood pressure, heart rate, cardiac index and total peripheral resistance data were averaged into five periods for analysis: baseline, stress task period, 25 – 30 min post-stress, 70 – 75 min post-stress, and 115-120 min post-stress. Data were analyzed using repeated measures analysis of variance, applying the Greenhouse-Geisser correction of degrees of freedom where the sphericity assumption was violated. Preliminary analyses assessed whether cardiovascular responses were influenced by the medication status of patients. There was no association between use of aspirin or statins and cardiovascular stress responses in the CAD group. Patients who had been taking β-blockers tended to be less stress reactive in blood pressure and heart rate, so prior use of β-blockers was included as a covariate in all cardiovascular analyses. Data were incomplete for some participants because of signal or equipment faults, so the number of participants analyzed was 38 for systolic and diastolic pressure, and 35 for heart rate, cardiac index and total peripheral resistance.

In addition to the repeated measures analysis of variance across trials, I also computed change scores between stress task trials and baseline, so as to assess stress reactivity. Stress reactivity may be influenced by factors other than group (CAD vs control) status,

including socioeconomic position, BMI, waist/hip ratio and use of β-blockers. These factors were therefore included as covariates in analysis of covariance on change scores.

The percentage of PLAs from each blood sample was calculated. Preliminary analyses indicated that PLAs were not affected by use of β-blockers, so this was not included as a covariate in analyses. PLAs were analyzed with group (CAD/healthy control) as the between-subject factor, and trial (baseline, stress, 30 minute, 75 minute post-task) as the within-subject factor. Responses to the stress tasks were further analyzed by calculating difference scores between baseline and stress trials, with income, BMI and waist/hip ratio used as covariates as these as parameters known to affect stress task responses.

The quoted F value represents the F-test which is used to determine if the variances in two samples are significantly different. The F statistic is calculated by dividing the larger variance by the smaller one. $F= (s^2_1) /(s^2_2)$. If the value of F exceeds the critical value for samples of the size under study ($p<05$) reject the null hypothesis of no difference.

Associations between subjective experiences during the session and cardiovascular and platelet responses were assessed using partial correlations, adjusting for the factors detailed in the results section. The relationships between depressive symptoms and cardiovascular and platelet responses were analyzed with linear regression, and the unstandardized regression coefficients with 95% confidence intervals are presented. Analyses were carried out using SPSS V 10.0.5, and data are presented in the tables and text as means ± standard deviation.

9.3 RESULTS

CAD patients and healthy controls did not differ in age (table 9.1). However, body mass index (BMI) tended to be greater in CAD patients (F (1,37) = 2.99, p = .092), and waist/hip ratio and per cent body fat were significantly greater in CAD patients than controls (F (1,37) = 14.2 and 4.15 respectively, $p < .05$). There was a tendency for CAD patients to report lower birth weights than healthy controls (F (1,25) = 3.00, p = .096). Similar proportions of patients and controls were married and in paid employment, and there was no difference in the number of hours worked per week. CAD patients were of lower socioeconomic status on both objective and subjective criteria; healthy controls had higher incomes ($\chi^2 = 7.65$, $p < .01$), and their ratings on the ladder measure were higher (F (1,37) = 4.22, $p < .05$). Only two of the participants were current smokers, but more CAD patients had smoked in the past ($\chi^2 = 7.14$, $p < .05$). Fewer CAD patients than controls drank alcohol regularly ($\chi^2 = 7.44$, $p < .01$), while scores on the sleep problems scale were greater in patients (F (1,37) = 6.97, $p < .05$). There was no group difference on the HAD depression scale, and only one individual scored above the threshold for clinically significant problems. HAD depression and sleep problems were positively correlated ($r = .51$, $p < .001$). In the light of the differences in socioeconomic status and body size between groups, income, BMI and waist/hip ratio were included as covariates in the cardiovascular analyses.

9.3.1 Cardiovascular stress responses

CAD patients and healthy controls did not differ in baseline blood pressure or heart rate. Levels measured manually averaged 118.4 ± 16.0 / 72.2 ± 10.8 and 117.0 ± 8.1 / 72.3 ± 5.4 mmHg in CAD patients and controls, while baseline Portapres levels averaged 117.6

± 15.8 / 72.1 ± 10.8 and 117.9 ± 8.6 / 72.2 ± 5.4 mmHg respectively, after adjusting for income, BMI, waist/hip ratio and use of β-blockers. Baseline heart rate averaged 64.7 ± 13.8 and 62.3 ± 7.4 bpm in the two groups.

Blood pressure responses over the session are summarized in Figure 9.1. There was a significant group by trial interaction in the analysis of systolic pressure (F (4,140) = 3.64, $p < .01$). The systolic pressure response to tasks was greater in the CAD patients, with mean increases of 43.9 and 28.3 mmHg in patients and controls (F (1,32) = 4.45, $p < .05$), adjusted for income, BMI, waist/hip ratio and use of β-blockers. *Post hoc* analyses indicated there were no differences between groups during the recovery phase. Analysis of diastolic pressure showed a main effect of trial (F (4,140) = 13.4, $p < .001$), but no interaction with group. The diastolic pressure responses to stress tasks averaged 21.6 and 15.7 mmHg in the CAD patients and controls, adjusted for covariates. Both systolic and diastolic pressure remained above baseline during the two hour post-task period in both groups. Results for heart rate are shown in Figure 9.2. The heart rate responses to stress tasks was greater in the CAD patients than controls (F (1,33) = 4.27, $p < .05$), with mean increases of 14.1 and 4.7 bpm adjusted for income, BMI, waist/hip ratio and use of β-blockers. Heart rate returned to baseline levels during the post-task period. Neither total peripheral resistance nor cardiac index differed between groups at baseline. The changes in total peripheral resistance and cardiac index over the session are summarized in Figure 9.3. Peripheral vascular resistance increased with stress then continued to rise in CAD patients but not controls. Analysis of covariance of the stress and post-task trials showed a main effect for trial in the CAD patients ($p < .05$) but not in controls. CAD patients had greater peripheral resistance increases than healthy controls between baseline and 30 minute post-stress, and baseline and 120 minutes post-stress (both $p <$ .05), but not for the 75 minute post-stress trial ($p = .093$).

Cardiac index also increased between baseline and stress task trials, so the blood pressure stress responses were sustained by a combination of raised peripheral resistance and cardiac output. The increase in cardiac index between baseline and stress trials was greater in CAD patients than controls (differences adjusted for income, BMI, waist/hip ratio and use of β-blockers. of 0.72 and 0.40 l/min respectively), but did not differ significantly. However, the subsequent decreases in cardiac index between baseline and 30 minutes and 75 minutes post-task were significantly greater in CAD patients than controls (F (1,29) = 6.66 and 7.53 respectively, $p < .05$).

9.3.2 Subjective stress responses

Subjective stress ratings showed a highly significant effect of trial (F (4,132) = 140.6, p <.001). As can be seen in Figure 9.2, ratings on the 7-point scale increased from an average of 1.4 to 4.36 during the stress tasks, returning to baseline levels in the post-task period. CAD patients and controls did not differ in ratings of task difficulty or task controllability, with averages of 5.53 ± 1.0 and 2.82 ± 1.0 on the two scales. However, CAD patients were significantly more involved with the tasks than healthy controls, with mean ratings of 6.12 ± 1.0 and 5.05 ± 1.4 respectively (F (1,37) = 7.52, $p < .01$).

9.3.3 Platelet activation

The percentage of PLAs was not related to income or to use of β-blockers, so data were analyzed with income, BMI and waist/hip ratio as covariates. CAD patients and healthy controls did not differ in PLAs at baseline, and there were also no differences in white blood cell or platelet counts. But the group by trial interaction was significant (F(3,87) = 5.50, p <.01), and is illustrated in Figure 9.4. The increase in PLAs in response to stress

was the same in the two groups, but they diverged in the post-stress period. PLAs remained high in the CAD patients, and returned to baseline levels in healthy controls. The difference between groups was significant at 75 minutes post-stress ($F(1,26) = 5.50$, $p <. 05$). Compared with baseline, the number of PLAs was an average 18.1% higher at 75 minutes post-stress in the CAD group, but had decreased by 9.3% in controls ($F(1,26) = 4.79, p <. 05$).

9.3.4 C-Reactive Protein

At rest CRP values were 1.93 ± 1.50 mg/l in the control group and 3.04 ± 2.8 mg/l in the CAD patients. Without adjustment there appeared to be a significant difference between the two groups but once adjustment was made for body mass index and waist-hip ratio, this difference disappeared. With stress the levels rose to 2.07 ± 1.62 mg/l in the control group and 3.10 ± 2.82 mg/l in the CAD patients. There was no significant difference between the increase between the two groups ($p = 0.364$) but there was an overall small but significant average rise of 4.8% in CRP over the course of the experiment ($F(1,30) = 5.04$, $p = 0.035$). There was a trend towards this rise being greater in the control group than in the CAD patients. The increase in CRP between baseline and 2 hours post-stress was positively correlated with the rise in PLA percentage between baseline and 75 minutes post-stress in CAD patients ($r = 0.68$, $p < 0.05$) but not in controls after adjusting for income, body mass index, and waist/hip ratio .

9.3.5 Associations between subjective factors and physiological responses

The stress-induced increases in both heart rate and cardiac index were positively correlated with increases in subjective stress between baseline and stress trials (partial *r*

= .41 and .46 respectively, p <.05, controlling for income, BMI, waist/hip ratio, use of β-blockers, and baseline heart rate or cardiac index). Larger cardiac responses were recorded from participants who showed greater subjective stress responses. Heart rate and cardiac index increases between baseline and stress trials were also positively correlated with ratings of task involvement (partial r = 0.46 and 0.37 respectively, p <.05). Changes in PLAs were not related to subjective stress ratings. However, there was a positive correlation between the PLA increase from baseline to 75 minutes post-task and ratings of task difficulty (partial r = 0.39, p < .05, controlling for income, BMI, waist/hip ratio, and baseline PLAs). Regression analyses indicated that heart rate stress responses were predicted by HAD depression independently of income, BMI, waist/hip ratio, use of β-blockers, and baseline heart rate (B = 1.03, C.I. .18 to 1.87, p <.05). A similar effect was observed for stress-induced increases in cardiac index (B = .09, C.I. .02 to .17, p <.025). In both cases, higher depression scores predicted heightened cardiac stress responses. HAD depression scores were not associated with blood pressure or PLA responses.

9.4 DISCUSSION

The principle findings of this study are as follows: CAD patients showed greater systolic pressure, heart rate and cardiac index responses to acute mental stress than age-matched healthy controls; total peripheral resistance increased during the post-task period in CAD patients but not in controls; platelet activation was stimulated by acute stress, and remained elevated for a more extended period after stress in CAD patients compared with controls; and cardiovascular responses were associated with subjective stress and with depression, while platelet activation was correlated with ratings of task difficulty .

Finally, CRP rose with mental stress and in CAD patients the increase was proportional to the increase in PLAs.

The two groups in this study were recruited using different methods. The healthy sample was recruited through their workplaces, while the CAD patients were identified from hospital registers. We made efforts to use identical methods of inviting people and providing information about the study, and neither group received any financial incentive. However, it is possible that patients with a diagnosed disease will approach a research study of this kind with different attitudes to those of healthy volunteers. Ratings of stress experienced before and during the tasks revealed no differences between groups, and they did not differ in ratings of task difficulty or task controllability either. There was one difference in that CAD patients reported greater task involvement than did the healthy group. It is difficult to evaluate the importance of this effect in the absence of differences on three other measures, but it is possible that clinical status affected appraisals of the situation. It should also be pointed out that because of the different recruitment methods, researchers were not blind to group membership. It is possible that subtle differences existed in how participants were treated. On the other hand, the absence of differences in subjective ratings between groups argues against this having been a strong effect.

The groups were comparable in age, resting blood pressure and haemodynamics, but there were significant differences in waist-hip ratio and in percentage body fat. The CAD patients had lower incomes on average than the controls and their self-rated socioeconomic status was lower. These differences were to be expected, since the incidence of coronary heart disease is inversely related to socioeconomic status, and is associated with abdominal obesity [588]. We have previously shown in other studies that

lower socioeconomic status predicts impaired post-stress recovery of blood pressure [587] and heightened post-stress total peripheral resistance [147], so this factor was included as a covariate in the analyses along with BMI and waist/hip ratio. The groups did not show any difference in depression, but sleep problem scores were greater in CAD patients than the control group. Associations between poor sleep and coronary heart disease have been described in a number of studies [589], and Leineweber et al [590] recently demonstrated that sleep problems predicted increased risk of recurrent cardiac events in women with ACS. Heavier persons and individuals with CAD are also at heightened risk from obstructive sleep apnea and disturbed sleep[591].

Systolic blood pressure increased by an average of 37% in the CAD patients compared with 24% in healthy controls. Heart rate increased by 21.7% versus 7.5% in controls. As noted earlier, variable results have been described in previous comparisons of CAD patients and healthy controls, with elevated blood pressure and heart rate stress reactions in some but not all studies. The computerized colour/word task was previously used in the Psychophysiological Investigations of Myocardial Ischemia (PIMI) studies, where systolic pressure increases averaged 21% in CAD patients [482] and 17% in healthy controls [486]. However, baseline systolic pressure in the two PIMI groups differed by 20 mmHg in that study owing to the presence of hypertension in a substantial minority of patients; a confounding factor removed in this study. It is unlikely that the differences we observed were due to cardiac patients finding the tests more stressful than the control group. Both groups were equally unfamiliar with the tasks and the assessment setting, and the low ratings of stress during baseline and recovery indicate that neither group reported apprehension or stress under resting conditions. The CAD patients did not show greater increases in subjective stress than controls. One explanation for the magnitude of responses may lie in the use of a continuous measure of blood pressure,

which may capture the dynamic profile of stress responses more accurately than sampling from a single cardiac cycle every one or two minutes, as is done with conventional cuff measures [568 592].

A critical issue in comparisons between CAD patients and healthy controls is medication. Almost all the patients in this study were taking aspirin and statins, and a substantial minority were prescribed β-blockers for cardioprotection. A review of 59 studies of the effects of β-blockers on cardiovascular reactivity showed effects on heart rate but not blood pressure responses [593]. In the present study, patients were withdrawn from β-blockers and statins 72 hours prior to stress testing. There was a tendency for patients who had been using β-blockers to be less stress reactive, but the number was too small to analyze as a separate group, so β-blockade was instead incorporated as a covariate. If β-blocker withdrawal was a factor then it was not likely to be at its maximum effect after 72 hours withdrawal [594], and for cardioselective drugs the increase in β-adrenergic sensitivity is small at 72 hours post-cessation. There is little sympathetic hypersensitivity following cessation of atenolol (the most commonly taken drug in our study population) therapy in normotensive CAD patients [595]. Beta-blockers do not change platelet aggregability during the sympatho-adrenal stimulus of mental stress [570]. As far as statins are concerned, lower cholesterol should if anything have reduced cardiovascular stress reactivity [562]. Our conclusion is that a genuine elevation of systolic blood pressure and heart rate stress reactivity is present in CAD.

It is possible that ACE inhibitors may have had some lingering effect on inflammatory measures. Ramipril the most commonly used ACE inhibitor has a short plasma half life of 7 hours but a long tissue life 120 hours [596 597], so the true haemodynamic effects may actually be more marked. All statins commonly used show very low systemic

bioavailability due to an extensive first pass effect at the intestinal and/or hepatic level. [598]. Atorvastatin shows the longest terminal half-life (11-14 h vs. 1-3 h), whereas the mean plasma elimination half-life is 1.8 hours for pravastatin[599]so statins are unlikely to have had any effect having been stopped for about 84 hours pre study

Blood pressure stress responses were sustained by a combination of changes in cardiac output and total peripheral resistance (Figure 3). The groups did not differ in their cardiac or vascular responses to tasks themselves, though there was a modest difference in cardiac index response which was presumably responsible for the larger systolic pressure response in the CAD patient group. During the post-stress period, a marked difference in haemodynamics emerged. Healthy controls maintained a moderately elevated total peripheral resistance offset by reduced cardiac index, resulting in small elevations in blood pressure in comparison with baseline. In CAD patients, there were substantially larger increases in peripheral resistance and correspondingly greater reductions in cardiac index. This vascular response is consistent with the results described by Sundin et al [557] in CAD patients. It may have potentially adverse effects on cardiac patients by increasing afterload. Stress-induced increases in peripheral vascular resistance have been associated with reductions in left ventricular ejection fraction [484]. Kop et al [509] reported that coronary artery constriction in response to mental stress was related to diastolic blood pressure reactivity, and this may be sustained by an underlying abnormality of coronary vasomotion secondary to endothelial dysfunction.

The increases in platelet activation with stress as assessed by PLAs in this study are consistent with earlier work using aggregometry and measures of α-granule proteins [457] [458] [570] [571]. Michelson and coworkers [573] have argued that circulating PLAs are more sensitive indicators of *in vivo* platelet activation than these measures or platelet surface

P-selectin. Circulating degranulated platelets rapidly lose surface P-selectin, yet continue to aggregate with monocytes and macrophages[574]. Increases of circulating PLAs but not P-selectin-positive platelets were observed in patients undergoing angioplasty, and have also been shown to be early markers of acute myocardial infarction [600]. Huo et al [601]have recently shown that injection of activated PLAs accelerated atherosclerosis in apolipoprotein E-deficient mice, promoting leukocyte binding of vascular cell adhesion molecule-1 and adhesion to inflamed endothelium.

The two groups did not differ in baseline PLA counts. Platelet function at rest has been shown to be similar in CAD patients and controls in previous studies [458]. The initial increase in platelet activation with stress was also the same in the two groups. But differences emerged in the duration of responses, with the increase in PLAs persisting 75 minutes post-stress in CAD patients, while returning to baseline in controls (Figure 4). The observation of a difference not in the magnitude but in the duration of stress-induced responses may explain why earlier comparisons of cardiac patients and healthy controls have shown mixed effects. These results are consistent with recent work suggesting that psychosocial risk factors for coronary heart disease are related to delayed post-stress recovery in other biological responses. For example, low socioeconomic status (a risk factor of coronary heart disease) is associated with delayed post-stress recovery of blood pressure and heart rate variability [587], and with prolonged elevations of Factor VIII and plasma viscosity [178]. The greater platelet activation 75 minutes post-stress is potentially important in the light of the evidence that episodes of anger are associated with increased vulnerability for the development of ACS for one to two hours [115].

It is interesting that these effects were observed despite use of aspirin by almost all CAD patients. Aspirin treatment has been shown to have little effect on platelet activation

with mental stress assessed by filtragometry or platelet factor 4 and β-thromboglobulin [359] suggesting that activation is not via a cyclo-oxygenase dependent pathway. Aspirin also fails to attenuate the PLA response to exercise [602] and has limited effect on activation by norepinephrine [603]. Recently it has been demonstrated that clopidogrel but not aspirin reduces both P-selectin expression and also the formation of PLAs in patients with atherosclerotic vascular disease [604]. It would seem therefore that aspirin is not an effective means of eliminating mental stress-induced platelet activation. However, it may be that greater differences between groups would have been seen in the absence of aspirin or upon aspirin withdrawal.

Individual differences in psychological responses were also associated with cardiovascular and platelet reactions. Heart rate and cardiac index responses were positively related to increases in subjective stress and to task involvement, while changes in PLAs were greater in participants who rated the tasks as being more difficult. These data indicate that in addition to clinical status, the individual's appraisal of the situation is related to biological responses. In the light of associations between depression and platelet activation in coronary heart disease patients [605], we expected that PLA responses might be related to depression. This was not the case, possibly because levels of depression in this sample were low. Nevertheless, HAD depression scores did predict stress-induced increases in heart rate and cardiac index independently of covariates. An association between depression in the non-clinical range and cardiovascular stress responses has been described in previous research on healthy women [148], so may be relevant to cardiac patients as well. In this study, we were not unfortunately able to assess heart rate variability which would have been interesting in the light of evidence relating impaired parasympathetic cardiac control with depression in post-infarction patients [213].

The modest rise in CRP with stress corroborates other investigators and reinforces the concept the mental stress is potentially a pro-inflammatory stimulus although no difference was seen between the groups after adjustment for BMI and waist/hip ratio. It may be that BMI and waist/hip ratio are major contributors to the increase cardiovascular risk of having a raised CRP. The finding that increases in CRP were proportional to increases in PLAs in the CAD group raises the interesting concept that the two processes may be triggered by a common pathway (such as adrenergic stimulation) or may be interdependent. It also suggests that in persons with a heightened psychobiological response to stress that there are several mechanisms that mediate a potential increase in risk of the manifestations of CAD. The rise in CRP with stress also may explain part of the increased cardiovascular risk in conditions such as depression, social isolation or low social status, all of which are equated as living under conditions of episodic or constant low-grade stress. Although no significant difference was seen in the increase in CRP to mental stress seen between the two groups it should be considered that there could be an effect on the inflammatory response with patients taking aspirin and that they had recently been taking statin medications which have been shown to attenuate CRP levels[606].

There is also new and increasing evidence that platelets may have an important role as inflammatory cells in addition to their importance in haemostasis. Activated platelets stimulate cytokines and express inflammatory markers [607]. They may also play a critical part in leucocyte and endothelial function as adhesion molecules and reactive oxygen species are also stimulated by platelet activation [608 609]. Therefore theoretically platelet activation could upregulate cellular adhesion molecules and cause increase white cell migration from the bloodstream into the intima stimulating atherosclerosis. Increased

reactive oxygen species may influence apoptosis of plaque stabilizing cells and stimulate matrix metalloproteinases thus increasing plaque instability and predisposing to plaque rupture [610]. Consequently the prolonged activation seen as a response to stress in the CAD patients may be important in the pathogenesis of both chronic and acute CAD.

This study has a number of important limitations. The groups were relatively small, and participation was limited to white male patients less than 60 years old. Greater numbers would have very likely given statistically stronger data. The exclusion of women is a major limitation. We were concerned that the inclusion of men and women would substantially increase the variability in measures of platelet function, and that with a small study of this type the effects of stress might be obscured. As noted earlier, the different methods of recruitment of CAD and controls resulted in groups that differed in socioeconomic profile, so that factor was taken into account statistically rather than through matching. The mean age of the CAD patients in this study is younger than most commonly found in clinical practice and it may be that more elderly patient would have a different response to mental stress than is shown here. The CAD patients had all recently been taking cardioactive medications, and these might have had enduring effects. Recent use of β-blockers was related to stress responsivity, but the sample was too small to analyze this as a separate factor. Although the cardiovascular monitoring continued for two hours post-stress, the last blood sample for the measurement of PLAs was taken 75 minutes post-stress. We do not therefore know whether the persistent elevation in platelet activation recorded from cardiac patients would have diminished after two hours. Nevertheless, the study indicates that CAD patients may show heightened cardiovascular responses to acute mental stress accompanied by prolonged platelet activation. These processes may be significant in the triggering of ACS and the development of complications in patients with advanced coronary atherosclerosis.

Table 9.1 CAD patients and healthy controls

Means ± standard deviation and N (per cent)

	CAD patients (n = 17)	Healthy controls (n = 22)
Age (years)	52.8 ± 4.5	50.2 ± 5.0
Body mass index (kg/m^2)	28.6 ± 5.4	26.1 ± 3.5
Waist / hip ratio	0.98 ± .08	.89 ± .07***
Body fat (%)	25.0 ± 5.6	21.3 ± 5.6*
Birth weight (kg)	3.39 ± .65	3.95 ± .94
Married	15 (88.2%)	17 (77.3%)
Paid employment	15 (88.2%)	22 (100%)
Work hours per week	49.0 ± 11.9	46.7 ± 7.8
Annual salary/income > £35,000	4 (23.5%)	15 (68.2%)**
Perceived socioeconomic position	6.1 ± 0.9	6.9 ± 1.5*
Current smokers	2 (11.8%)	0
Former smokers	10 (66.7%)	5 (22.7%)*
Alcohol consumption		
Never	3 (17.6%)	0
Less than daily	9 (52.9%)	7 (31.8%)
Daily	5 (29.4%)	15 (68.2%)**
Physical activity (days/week)	2.56 ± 1.9	2.27 ± 2.0
Average sleep hours	6.69 ± 1.2	6.66 ± .70
HAD depression	4.18 ± 2.9	3.36 ± 3.4
Sleep problems	9.55 ± 5.3	5.86 ± 3.5*

* p <.05, ** p <.01, *** p <.001, for differences between groups

Figures

Figure 9.1 Mean systolic blood pressure (upper panel) and diastolic blood pressure (lower panel) for five periods: baseline, average of task trials, and 25-30 min, 70-75 min and 115-120 min post-stress. Solid lines = CAD patients; dashed lines = healthy controls.

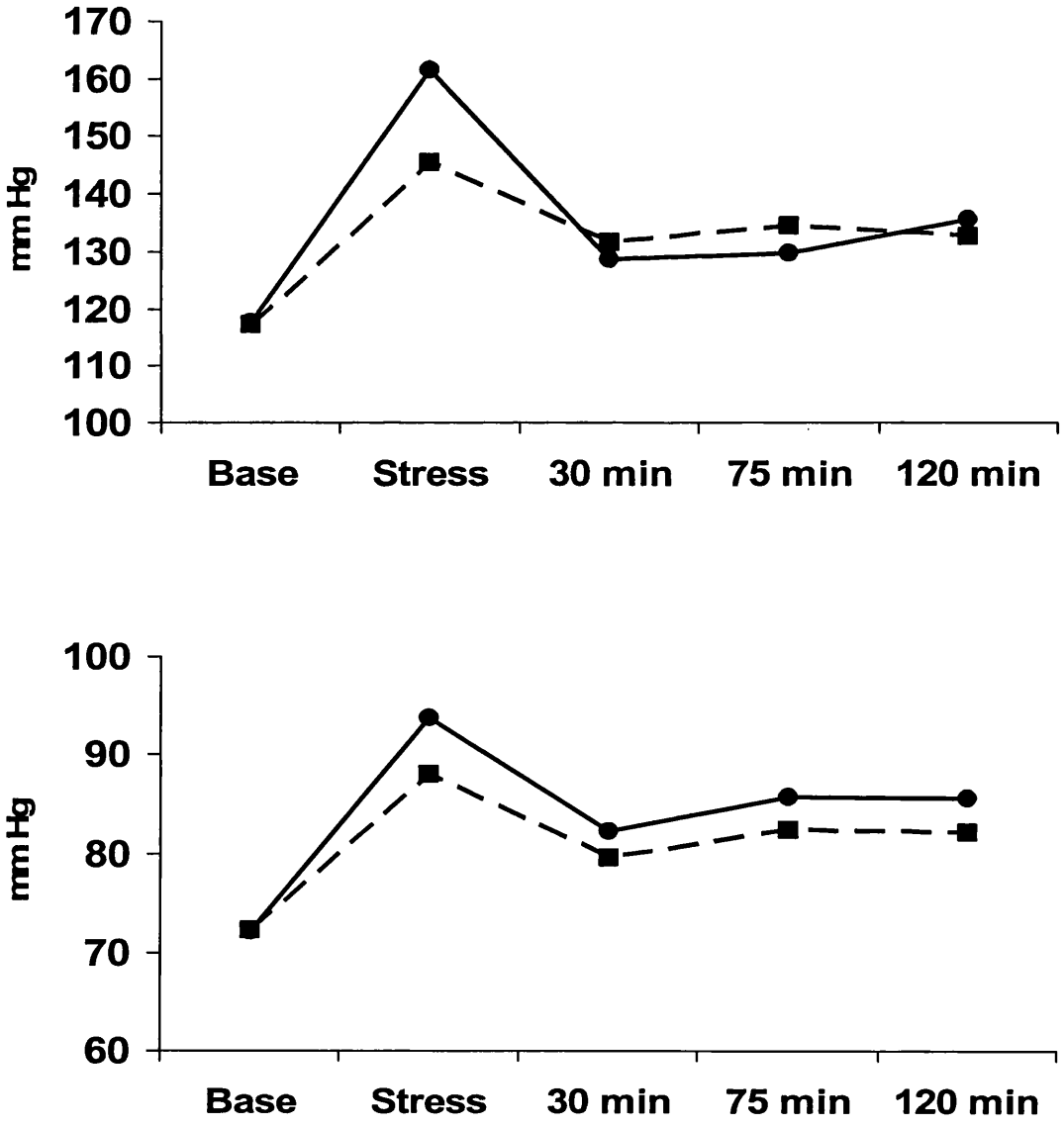


Figure 9.2 Mean heart rate (upper panel) and subjective stress (lower panel) over the five trials. For details, see legend to Figure 1. Solid lines = CAD patients; dashed lines = healthy controls.

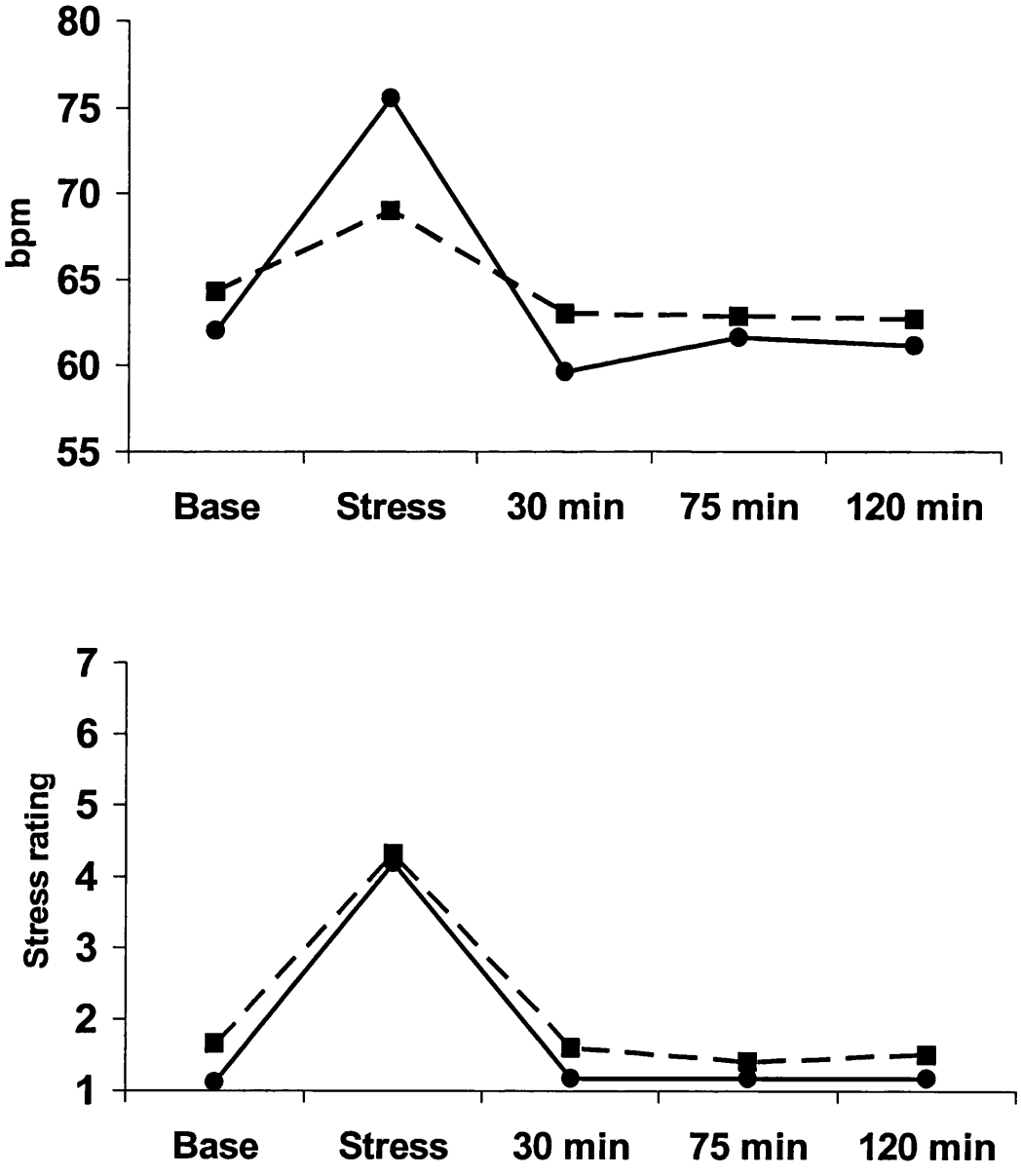
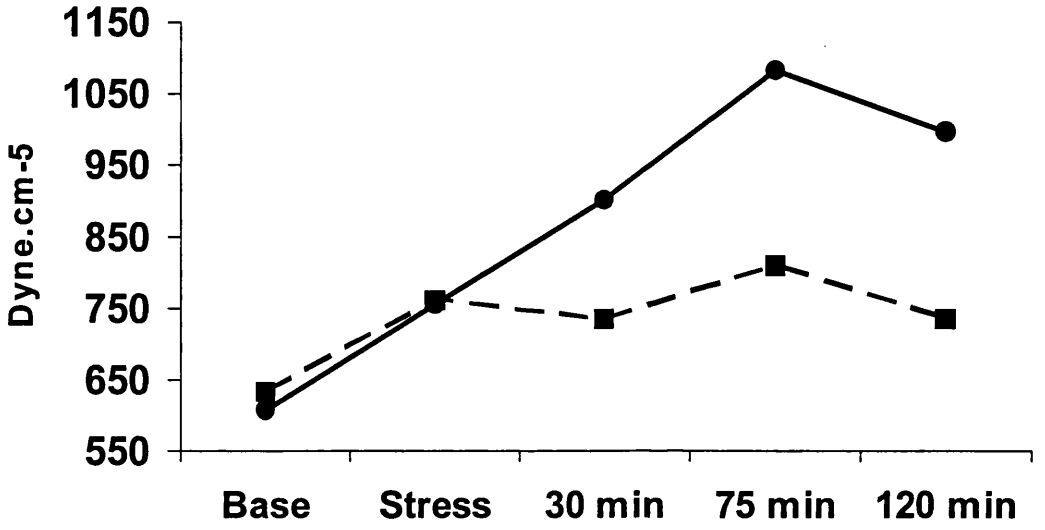


Figure 9.3 Mean total peripheral resistance (upper panel) and cardiac index (lower panel) over the five trials. For details, see legend to Figure 1. Solid lines = CAD patients; dashed lines = healthy controls.



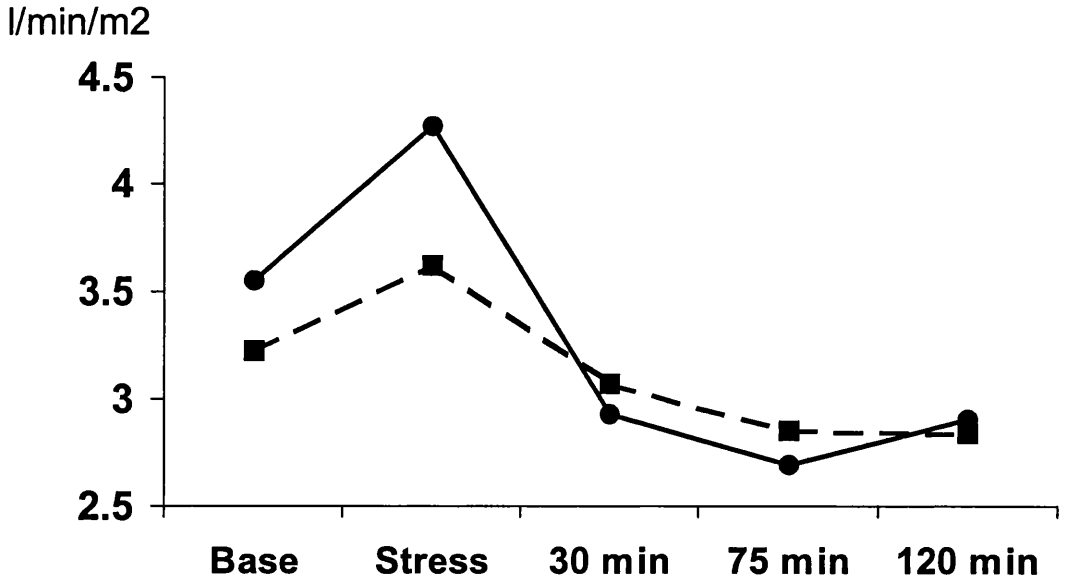
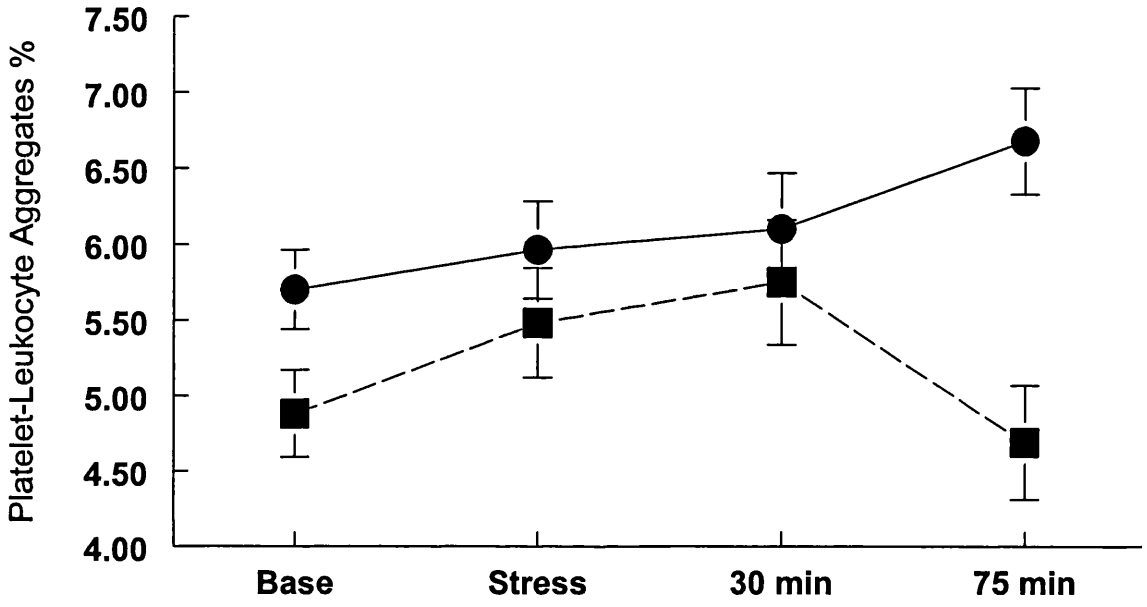


Figure 9.4 Mean percentage of PLAs at baseline, stress, 30 min post-stress and 75 min post-stress. Solid lines = CAD patients; dashed lines = healthy controls. Error bars are standard error of the mean.



Chapter Ten

THE LABORATORY INVESTIGATION OF PSYCHOPHYSIOLOGICAL REACTIVITY IN PATIENTS POST-ACS

10.1 INTRODUCTION

As noted in chapters 3, 6 and 9, the vast majority of work examining psychophysiological reactivity has been done on groups of healthy volunteers or on patients with stable CAD. Consequently there is no objective evidence examining psychophysiological reactivity focusing on patients who have sustained ACS.

The current literature is inconclusive about the role of psychophysiological reactivity (see Chapter 9) in the pathogenesis of chronic and acute cardiovascular disease. In Chapter 9, evidence has been presented that there is exaggerated haemodynamic and platelet psychophysiological reactivity in CAD patients compared with normal controls. In the ACCENT study (Chapters 7 and 8), the role of psychological factors as triggers of ACS has been demonstrated and several psychosocial factors have been identified that moderate this effect. The mechanisms by which these factors influence the occurrence of ACS are still unknown. Other important unresolved issues are whether an individual's psychophysiological reactivity can be linked to emotionally-triggered ACS and how is this affected by other psychosocial factors.

Psychophysiological reactivity has been linked with several mechanisms implicated in acute cardiovascular disease. It has related to haemodynamic response [555-557], coronary arterial vasoconstriction [508 509], platelet reactivity [359 458 550], fibrinogen[184], interlekin-6 [449], CRP (see Chapter 9) and lymphocyte count[611]. Similarly, there are several negative studies as well [436 497]. These variables are further modified by interactions with psychosocial factors such as socio-economic status and work stress [161 178 184]. There may also be an interaction between individual physiological mechanisms in response to psychological stress as suggested by the interaction between CRP response and platelet reactivity in CAD patients seen in Chapter 9.

If exaggerated psychophysiological stress responses are implicated in a proportion of patients with stress-triggered ACS then it might be possible to use pharmacological or cognitive behavioural therapy to try and reduce the subsequent cardiovascular risk of these patients. It may be possible to screen patients to identify a specific at risk population who might benefit from such an intervention. For example, in the ENRICHD trial, CBT was only successful in the sub-group of white males [227]. Clearly other programmes to target other gender and ethnic populations should be trialled. Even if only a small percentage of those who suffer ACS annually could be helped by targeted interventions then this would still potentially translate into a huge reduction in morbidity and mortality.

One of the objectives of this thesis (chapter 1) is "To examine whether patients with ACS triggered by acute psychosocial factors have an altered psychobiological reactivity compared with non-triggered ACS patients". The ACCENT cohort of 263 patients post ACS provided an ideal group to allow comparisons of triggers and psychosocial factors

to be made as the clinical data on admission, as well as detailed interview data regarding the circumstances surrounding ACS onset were available. In this chapter, this information is combined with data from a laboratory stress study to correlate psychobiological reactivity with ACS triggering and clinical findings.

The main hypothesis being tested in this study was the following:

1. Patients whose acute coronary admissions were triggered by emotional factors would show either heightened haemodynamic and platelet stress reactivity in the laboratory, or delayed post-stress recovery, in comparison with ACS patients who did not experience emotional triggering.

In addition, two subsidiary hypotheses were tested:

2. Patients who underwent standardised mental stress testing following acute cardiac admissions would show a similar pattern of psychophysiological response to that observed in Chapter 9: namely a) marked increases in blood pressure sustained acutely by increases in both cardiac output and total peripheral resistance; b) continued elevation in blood pressure above baseline in the post-stress recovery period due to sustained increases in peripheral resistance, and c) platelet activation as indexed by PLAs that is maintained for at least 75 minutes post-stress. In the present experiment, PLAs were also measured 2 hours post-stress, so as to discover whether levels returned to baseline by that point.
3. Lower SES participants would show greater psychophysiological reactivity than higher SES patients.

This experiment was not started until a few months before my thesis was completed, and recruitment of patients was slow (for reasons described below). The results of

just 20 patients are therefore described. More patients will be included in this experiment at a later date. The findings must therefore be regarded as preliminary, and several issues cannot be fully addressed, as detailed in later sections of the chapter.

10.2 METHODS

10.2.1 Participants

Participants were taken from the 263 patients recruited in the ACCENT study (Chapter 7 and 8). It was hoped that we would be able to study as many patients as possible in a drug free state and so strict exclusion criteria were established to provide a safe study group with minimal confounding factors. It is important to bear in mind that the ACCENT patients were already a highly selected population to avoid confounding influences of infectious, inflammatory or neoplastic conditions.

Exclusion criteria were

1. Ongoing symptoms of chest pain or breathlessness
2. ACS, coronary angiography, angioplasty or coronary artery bypass surgery within the preceding 6 months
3. Severely impaired left ventricular function
4. Age over 80 years
5. Any new significant co-morbid problems that may affect haemodynamic, haematological or biochemical measurements
6. Medical reasons not to stop medication
7. Hypertension

8. Atrial fibrillation or history of late ventricular dysrhythmias
9. Colour blindness
10. Night workers

Rationale Behind Exclusion Criteria.

It was considered unsafe and unethical to discontinue medication in patients with ongoing cardiac symptoms, hypertension, recent ACS, PCI or CABG, or severely impaired LV function. Similarly it was not considered appropriate to remove patients from medication needed for other conditions, for example discontinuing aspirin in a patient with a history of transient ischaemic cerebral events. Patients with atrial fibrillation were excluded as their haemodynamic data would not be necessarily compatible with patients in sinus rhythm and because of the likelihood that they would be taking negative chronotropes and negative inotropic drugs thus making haemodynamic responses difficult to interpret. Night workers were excluded because of the difference that would be found in their diurnal physiological rhythms and patients with colour blindness were excluded as they would be unable to perform the Stroop colour / word interference task.

Ethical approval was sought from the Ethics committees of the three recruiting centres. University College London NHS trust and Southend Hospital approved the plans to withdraw fully informed and consented patients from their medication. St George's Hospital Ethics committee however refused consent for this as the committee felt it was unethical to ask patients post ACS to stop taking beta-blockers. Therefore patients from St George's were asked to stop taking aspirin and other cardio-active medications but to keep taking beta-blockers as normal. It was hoped that these patients might give us

information on the efficacy of beta-blockers in preventing or modifying any of the physiological effects of mental stress. This issue will be addressed when the experiment is complete, but there are not sufficient cases at present to carry out the analyses.

All patients were considered for invitation to participate. Potentially suitable patients then had their hospital records checked to ensure that there were no other problems that might exclude them from the study or might make participation dangerous. Particular attention was paid to whether there was heart failure or serious impairment of left ventricular function post infarction, whether the patient had had any arrhythmias, and whether there had been any other subsequent complications or co-morbid problems. Patients who had undergone coronary angiography had their details reviewed to ensure that there were no severe untreated lesions which may potentially cause problems if medication was temporarily omitted. Suitable participants were then written to with an invitation to participate and were sent a patient information sheet detailing the rationale behind the study as well as the laboratory procedure and any potential complications (see appendix xi for invitation letter, appendices xii and xiii for patient information sheets). Potential participants were then telephoned about 10 days subsequent to receiving the information to explain the study, answer any questions and to solicit participation in the study.

Because of the small risk inherent in cardiac patients stopping their medication even for a short while, a clearly worded and explicit account of potential risks was included in the information sheet. It was an ethics committee requirement that we calculate a finite risk of adverse events and quote this on the information sheet. Trial data does not exist that specifically looks at the patient population that we are dealing with. Our population was

extremely different from the CAD populations in whom there are death and adverse event data on drug withdrawal. All our patients had had ACS, the vast majority had had percutaneous or surgical revascularisation, hypertensives were excluded and there were strict co-morbidity exclusions.

There are also no data concerning combinations of medications. Very few studies are now able to have unmedicated patients with CAD as controls. Our study population was effectively a stable CAD population post ACS. For risk estimate we used the whole population data from the HOPE (Heart Outcomes Prevention Evaluation) trial of ACE inhibitors post AMI [612], the 4S (Scandinavian Simvastatin Survival Study) trial of simvastatin post AMI[613], the Norwegian Timolol Trial for beta-blockade post AMI[614] and the SAPAT (Swedish Anginal Pectoris Aspirin Trial) trial of aspirin in stable angina [615]as there are no data concerning withdrawal of aspirin in a post ACS or AMI group. Hopefully as our patients had mostly been revascularised then they fell into a much lower risk group than any of these studies but it was felt that the highest risk should be quoted to patients. We also estimated a cumulative risk for each medication; one would assume this was higher than for withdrawal from a combination of drugs. It is important to bear in mind that this will be a large over-estimate of risk as our population will include no recent ACS, no hypertensives and importantly no patients with poor left ventricular function population (a powerful predictor of post ACS death and adverse events[616]). There is also no decisive evidence on beta-blocker withdrawal and stroke in non-hypertensive patients. Because of the time taken for platelet function to return to normal after cessation of aspirin therapy [617] patients were asked to stop taking aspirin ten days before their appointment for mental stress testing. Using data from the SAPAT trial [615], a randomised double blind placebo controlled trial of aspirin use in chronic stable angina patients, the excess absolute risk of death, non-fatal MI or stroke during a 10 day

period free of aspirin is 0.064% or 1 in 1563 patients. These figures are likely to be a significant overestimate of the risk as there will be an aspirin effect on the overall platelet function for several days after stopping aspirin therapy so this represents a worse case scenario. Using a similar rationale, the risk of a major adverse event in three days abstinent from ACE inhibitors is 0.006%, from beta-blockers is 0.033% and from a statin is 0.016%. Thus in a high risk individual on all of the above medication the worst risk of an adverse event for stopping aspirin for 10 days and a statin, ACE inhibitor and beta-blocker for 72 hours would be in the order of 1 in 840 (0.119%).

If patients agreed to participate then a date was agreed with the patient at that time. Patients again had the study explained verbally on the telephone. Participants also underwent a brief telephone interview to double check that they were suitable to participate and that there would be no excess risk in stopping their medications. Verbal consent to study participation was taken at that point on the telephone. Participants were reimbursed for their travel expenses but no other payment was made.

10.2.2 Measures and behavioural tasks

Haemodynamic variables (blood pressure, heart rate, cardiac output, total peripheral resistance and stroke volume were monitored continuously from the finger using a Portapres-2 [580] using the methods outlined in Chapter 9. Weight, height and waist and hip circumference were measured with standard methods, and body fat was assessed using a Bodystat® 1500 bioelectrical impedance body composition analysis device (Bodystat Ltd, Douglas, Isle of Man). Questionnaires were used to collect data on demographic and social factors as in Chapter 9.

Psychological stress was induced by two behavioural tasks previously used in this laboratory [587]. The first was a computerized colour-word interference task developed at the University of Pittsburgh involving the consecutive presentation of target colour words (e.g. green) printed in another colour. At the bottom of the computer screen were names of four colours printed in incongruent colours, and the task was to press a computer key that corresponded to the position at the bottom of the screen of the name of the colour in which the target word was printed. The rate of presentation was automatically adjusted by the computer to ensure sustained demands. The second task was a public-speaking task. The main studies in the literature with data on psychophysiological reactivity in patient with CAD are the PIMI studies looking at mental stress-induced myocardial ischaemia (see chapter 6)[475 482 486 526]. To try and get some sort of comparability with their data it was decided to use the same mental stress tasks in this study as they had used. Participants were given a sheet of paper with an imaginary scenario where they had incorrectly been accused of theft and had to make a speech in their defence (see appendices xvi and xvii for scenario instructions). Participants had 2 minutes to read the sheet and then a further 3 minutes to make preparations to give the speech. Participants were told that the speech was being video-taped and that it would be later marked for content. They were asked to speak for the full 3 minute period and to avoid hesitation or repetition. They were then asked to give the speech to a camera with one of the researchers also present in the room.

10.2.3 Measures of platelet function

Platelet function was measured in an identical fashion to Chapter 9. However as a persistent elevation in PLAs had been noticed at 75 minutes post stress in the study in

Chapter 9, a further assessment of platelet function was added at 120 minutes after completion of the stress tasks.

10.2.4 Procedure

Participants were asked to refrain from taking their usual cardiac medication as previously specified. Non-cardiac drugs were continued up to the morning of the study. Diabetic medication was taken as normal if required. Participants were asked to not use non-steroidal anti-inflammatory drugs and to take paracetamol if they required non-cardiac pain medication. All sessions were carried out in the morning beginning at 9.00 am. Participants were instructed not to have drunk tea, coffee, or caffeinated beverages on the morning of the experiment, not to eat a high fat or high protein breakfast, and not to have consumed alcohol or exercised on the evening before or the day of testing (see appendices xiv and xiv for patient session instructions). All patients gave written consent (appendix xviii) At the beginning of the session, anthropometric measures were taken, a venous cannula was inserted, and the participant rested for 30 min. Blood pressure and heart rate were recorded for the last five minutes of the rest period using the Portapres, after which two readings were obtained manually with an electronic sphygmomanometer, and the baseline blood sample was drawn. The laboratory protocol is included as appendix xix.

The participant rated feelings of stress on a 7-point scale from 1 = *low* to 7 = *high*. The two tasks were then administered each for five minutes in fixed order beginning with the colour-word interference task. Blood pressure and heart rate were recorded continuously during tasks. At the end of each task, the participant rated task difficulty, involvement, controllability and feelings of stress on 7-point scales from 1 = *low* to 7 = *high*. A

second blood sample was drawn immediately after the second task. The participant then rested quietly for the remainder of the experimental session. Five minute recordings of blood pressure and heart rate were made 25 – 30 min, 70 – 75 min and 115-120 min post-stress, and further blood samples were drawn 30 min, 75 min and 120 min post-stress. Laboratory investigators were blinded to the clinical details of the study volunteers and whether they had had emotionally triggered ACS.

10.2.5 Statistical analysis

The blood pressure, heart rate, cardiac index and total peripheral resistance data were averaged into five periods for analysis: baseline, stress task period, 25 – 30 min post-stress, 70 – 75 min post-stress, and 115-120 min post-stress. Data were analyzed using repeated measures analysis of variance, applying the Greenhouse-Geisser correction of degrees of freedom where the sphericity assumption was violated.

Two sets of comparisons of psychophysiological stress responses between subgroups of participants in the study were carried out. First, the relationship between stress responses and SES was analyzed by comparing the deprivation groups described in chapter 7 (section 7.7), and by analyzing participants varying in educational attainment. Second, comparisons were made between participants with and without emotional triggers of their ACS. In the SES analyses, multiple regression analysis of stress responses were carried out, with the SES marker (deprivation or education), age, smoking, BMI and baseline activity as independent variables. In the comparison of patients with and without emotional triggers, the main analytic method was repeated methods analysis of variance, with group as the between-subject factor and trial as the within-subject factor.

Analysis of covariance also used to determine whether associations between grouping factors (SES or emotional triggering) and physiological responses were independent of confounders. Analyses were carried out using SPSS V 10.0.5, and data are presented in the tables and text as means ± standard deviation. In the Figures, error bars are standard errors of the mean (s.e.m.).

10.3 RESULTS

10.3.1 Laboratory Patient Demographics

Of the 263 patients who were screened 136 were excluded. 59 additional patients were still within 6 months of their original ACS, PCI or CABG. The reasons for these exclusions are shown in table 10.1. 48 patients declined to take part leaving a study population of 20 patients. The final study population was completely comprised of male participants. No suitable female participants agreed to take part in the study. The demographics of these patients is shown in table 10.2

The population had a young mean age of 56.05 with an age range of 39 to 73. This group has a younger mean age than the mean age of the entire ACCENT study population (mean age overall 60.0 years, 58.5 years for men). Older patients were more likely to have co-morbid problems excluding them from invitation or preventing them from attending for study. The study group had a high mean BMI of 29.50 (mean overall for the ACCENT population = 27.0, for men = 27.3) and waist-hip ratio of 1.02. The study population was exclusively made up of white participants. No suitable non-white participants agreed to participate. There was a high incidence of hypertension and of

other co-morbidities including cerebrovascular disease in the non-white group which limited suitability for study.

The level of education amongst the laboratory participant was different overall from that of the entire ACCENT study population. Participants were more likely to have a higher level of education (40% versus 33% in the ACCENT study). Patients were also more likely to have a low deprivation index of 0 (60% versus 44.1 %). It is well documented that more educated people are more likely to participate in research [185] and this can potentially bias findings if not controlled for. Part of this may be due to the fact that there is a link between low social status and health and patients from lower socio-economic groups might be expected to have a greater incidence of co-morbidity preventing study. There were fewer current smokers in the laboratory study population than in the ACCENT study population (25% current smokers in this population compared with 44.3% of men in the ACCENT population). However a further 5 patients had recently stopped smoking and they were considered with the current smokers for analysis as most of these patients had been smoking at the time of their ACS. This makes the assessment of the effect of smoking difficult because of this inconsistency. The ratio of STEMI versus NSTEMI was similar to that of the ACCENT study. No patients had had previous MI and no patients had sustained heart failure. These patients were largely excluded by examination of angiographic and echocardiographic data excluding patients with poor left ventricular function.

The mean time from ACS to laboratory testing was 15.6 months. 12 patients had undergone percutaneous coronary intervention post ACS, 3 had had CABG and 5 had received medial therapy. All patients were chronically medicated, all took aspirin, 19

took statins, 19 took ACE inhibitors and 11 took beta blocker therapy. 5 patients from St George's were taking beta-blockers at the time of mental stress testing.

10.3.2 Complications

One participant suffered from sensations of palpitation when stopping medication (ACE inhibitor and statin, not beta-blocker therapy). He was seen at his local hospital and no sinister cause was found but the patient declined to take further part in the study. One patient had a vasovagal episode at the end of testing. His cannula had tissued and upon taking a final sample via a new cannula, the patient became sweaty, unwell and then syncopal. He was laid supine and placed on a cardiac monitor which showed sinus bradycardia. He was one of the St George's patients who had remained on beta-blockers for laboratory testing. He recovered in a few minutes and was then observed in the nearest Accident and Emergency department to ensure that no ill effects had occurred. He was discharged later that day and has remained well since.

10.3.3 Physiological Stress responses – Haemodynamic Responses

The data showing the haemodynamic responses to the stress tasks are presented in table 10.3 and are illustrated in Figures 10.1 to 10.3. There is a significant effect of trial for systolic and diastolic blood pressure, heart rate, cardiac index and total peripheral resistance ($F(5,90) = 33.6$, 24.0, 33.1, 20.6 and 7.07 respectively, all $p < .001$) , whereas there is no significant difference seen in stroke volume over the course of the laboratory session ($F(5,85) = 1.99$, $P = 0.13$). The increase in blood pressure seen is mediated by increased total peripheral resistance as well as an increase in cardiac output during the

stress trials. The increase in cardiac output is mediated by an increase in heart rate as the stroke volume index does not significantly alter. This pattern and magnitude of haemodynamic changes seen are similar to those seen in the patients with CAD studied in Chapter 9 with CAD patients displaying an exaggerated acute haemodynamic stress response compared with healthy volunteers. Public speaking did not cause as great a haemodynamic response as we had expected, although there was a tendency for greater systolic blood pressure, cardiac output index and heart rate rises with the public speaking test and a trend towards a greater rise in total peripheral resistance and lower stroke volume index with the Stroop test. Other researchers have shown much larger reactions to speech than other tasks [482], but this was not the case in the present experiment. There was only partial recovery of blood pressure responses during the post-stress period. At 2 hours post-tasks, both systolic and diastolic blood pressures, although significantly lower than during stress were still significantly higher than they had been at baseline. The acute haemodynamic changes with stress are very close to those found in the PIMI study [482].

Similarly to the systolic blood pressure response, the heart rate rose with the Stroop test and then rose further with the public-speaking test. This is in keeping with published comparisons of the 2 tests [482]. At 2 hours post stress tasks, the mean heart rate had fallen to a significantly lower level than at baseline. However at this 2 hour time, systolic and diastolic blood pressure and total peripheral resistance were still all significantly elevated compared with baseline. Cardiac index increased during the stress tasks and then fell below baseline in the recovery period (figure 10.2). This mirrors a trend seen in the graph of stroke volume index after the stress tasks (figure 10.3) where stroke volume index is lower at the end of the session than at baseline. In contrast to this, total peripheral resistance increased with stress and sustained the increases during the recovery phase. This pattern of increase in cardiac index and total peripheral resistance is

similar to that documented in Chapter 9. Consequently, acute blood pressure responses during stress are sustained by a combination of heightened cardiac output (mostly mediated by increased pulse rate) and increased peripheral vascular resistance. However, continued elevation in peripheral resistance maintains the elevated blood pressure seen in the recovery phase.

10.3.4 Physiological Stress responses – Platelet Responses

The platelet responses to stress are shown in table 10.4 and are depicted graphically in figure 10.4. There is an overall PLA increase to mental stress as was seen in Chapter 9 ($F(4,72) = 5.35$, $P = 0.003$). However in this study we analysed PLA responses at an extra time point of 120 minutes as well as the previously final time point of 75 minutes in Chapter 9. The present results indicate that the platelet stress response was maintained at 2 hours post stress. There is no clear sign of recovery even at this point, suggesting a longer period of physiological vulnerability than was previously thought. In terms of the component white blood cell aggregates, the different types of aggregate show fairly similar patterns except that there is some sign that the platelet-monocyte aggregates are beginning to decline at 2 hours ($F(4,72) = 2.00$, $P = 0.14$ for PL – monocytes, $F = (4,72) = 4.35$, $p = 0.014$ for PL – neutrophils, $F(4,72) = 7.59$, $p = 0.001$ for PL – lymphocytes).

10.3.5 Subjective Stress Responses

Participants rated both mental tasks as stressful ($F(5,95) = 35.15$ $p < 0.001$ compared with baseline) with slightly more stress being induced by the public-speaking task.

Subjective perception of stress was not related to education, deprivation or to any of the physiological responses measured.

10.3.6. Cardiovascular Responses and Socio-economic Factors

The comparison of the deprivation groups showed interesting differences in systolic blood pressure and heart rate. Regression analysis indicated that systolic blood pressure responses to the mental stress tasks were greater in the more deprived individuals independently of age, BMI, baseline blood pressure and cigarette smoking B = 10.5, 95% confidence interval = 0.14 to 20.9, p = 0.047. The adjusted mean systolic pressure increases ranged from 27.6mmHg in the least deprived to 47.7mmHg in the most deprived, indicating that systolic blood pressure reactions were 72.8% greater in the most deprived group. The results for diastolic blood pressure were in the same direction but not significant (p = 0.099). The rate of haemodynamic recovery was also inversely proportional to the level of deprivation. There was a higher heart rate level seen in the most deprived participants at the first post-stress recovery assessment (25-30 minutes), after controlling for age, body mass index, baseline heart rate and smoking status B = 3.11, 95% confidence intervals = 0.34 to 5.88, p = 0.031. No association between platelet activation and deprivation was observed. Nonetheless, these analyses indicate that haemodynamic stress responses and post-stress recovery may be disturbed in patients of lower SES.

10.3.7. Platelet Responses and Socio-economic Factors

Although there was no effect on the PLA responses seen with variation in deprivation index, associations were observed with educational attainment. The predictors of the increase in PLAs with stress were analysed using multiple regression. Independently of baseline PLA, age, BMI, waist-hip ratio and smoking, less educated participants showed larger PLA increases to mental stress, B = - 0.74, 95% confidence interval = -1.20 to -0.29, p = 0.004. The change in PLAs in the least educated group (no qualifications) was greatest at 1.15 ± 0.95, in the middle group was 0.61 ± 0.37, and was least in the most educated group (educated at A level or above) at 0.24 ± 0.94. Although the acute PLA response was greater in less educated participants, there was no difference between the groups in the persistence of PLA elevation.

These data suggest that there is a greater haemodynamic and haematological reactivity to stress in patients with markers of lower socio-economic status. This is analogous to work previously done in this department in healthy civil service volunteers, but here in patients post ACS [579]. Importantly, there was no difference in the perceived stress that was induced by the stress tasks and either deprivation or educational achievement. Thus it is not the case that lower SES participants were psychologically more stressed by the tasks.

10.3.8 Physiological Stress Reactivity and Emotional Triggering

Because of the small number of participants in this study and particularly because of the small number of patients who had ACS triggered by the individual triggers of anger, stress and depression, all 3 of these emotional triggers were considered together for

statistical analysis. Of the 20 participants who underwent laboratory stress testing, 7 had experienced emotional triggers in the two-hour hazard period before their ACS and not in the control period. Thus, this group (the "trigger group") and the remaining patients (the "non-trigger group") were compared to see if there were any differences in physiological stress responses that differentiated the two groups.

There was no significant difference in either the blood pressure or heart rate responses to stress between the two groups, ($F = 0.91$, $p = 0.36$) although the blood pressure at rest in the trigger group was non-significantly higher than the non-trigger group (127.2 versus 119.2 mmHg). The one haemodynamic variable that was different between the two groups was cardiac output ($F = 7.29$, $p = 0.018$) independent of age, body mass index and smoking. There was also a trend towards slower haemodynamic recovery in the trigger group. Trigger patients had a significantly higher cardiac output throughout the study after adjusting for BMI, age and smoking for both baseline and task trials ($p = 0.021$), although neither heart rate nor stroke volume were individually statistically greater. The blood pressure responses and cardiac output responses to stress in the trigger and non-trigger patients are shown in figure 10. 5.

At baseline, before mental stress there was no difference in overall percentage of PLAs (or any subsets) between the trigger and the non-trigger groups. However a difference between the two groups became apparent with mental stress. In the PLA analysis, the response to tasks was significantly greater in the emotional trigger group than the non-trigger group after controlling for baseline PLA, age, BMI and smoking ($F = 4.91$, $p= 0.045$). This pattern is seen in figures 10.6. As well as the significant effect for PLAs overall, there was a similar significant effect in the analysis of platelet-neutrophil

aggregates ($F = 6.23$, $p= 0.027$) and an effect on platelet-lymphocyte aggregates that approached significance ($F = 3.80$, $p = 0.073$). These differences in PLAs increase remained throughout the two-hour period post stress. Interestingly the effect upon platelet-monocyte aggregates was not significant. Again, it is important to underline the fact that the physiological differences seen were not due to any perceived difference in the stressfulness of the tasks.

10.4. DISCUSSION

This small laboratory study has confirmed the pattern of mental stress induced physiological response in patients post-ACS. There is a rapid and pronounced increase in systolic and diastolic blood pressures, cardiac output, heart rate and total peripheral resistance with the onset of mental stress. This pattern of haemodynamic change suggests an increased risk of acute cardiac events mediated by increased shear stress within the arterial tree, increased afterload, increased myocardial workload and potentially increased coronary vasoconstriction. Haemodynamic responses were more pronounced and prolonged in more deprived patients. It may be that the prolonged haemodynamic abnormalities predispose to increased atheroma development.

Platelet aggregability to mental stress was heightened in patients who had experienced emotional triggers for their ACS, and this is likely to be a key mechanism by which acute psychosocial triggers are translated into acute clinical events. Increased platelet aggregability was also found in less educated patients. This may play a part in the social gradient in acute and chronic cardiovascular disease observed by many studies (see Chapter 3).

However, it should again be emphasised that because of the small number of participants, these findings must be regarded as preliminary, and only suggestive of differences between groups. Further corroborative evidence should hopefully emerge from the study of future participants.

The data are comparable with those found in Chapter 9 with increased blood pressure being maintained by increased peripheral resistance. The fact that two brief stress tasks totaling less than 10 minutes causes a significant haemodynamic effect upon systolic and diastolic blood pressure, total peripheral resistance and cardiac output lasting at least 2 hours is a notable finding. This ties in with the work of Ghiadoni et al [154], who found that endothelial function was abnormal with impaired endothelial dependent flow mediated dilatation up to 90 minutes after acute mental stress. People who have repetitive episodes of even brief mental stress may in fact have abnormal haemodynamics with increased blood pressure and total peripheral resistance for recurrent prolonged periods and this, especially if accompanied by impaired endothelial functioning may provide a basis for initiation and progression of atherosclerotic vascular disease. If endothelial dysfunction is responsible for the altered pattern of haemodynamic responses observed then it may also be responsible for the alteration in platelet aggregability as the healthy endothelium inhibits platelet activation by nitric oxide production. Ghiadoni et al[154] found that endothelial function had recovered by 240 minutes post stress so the true time of acute stress induced dysfunction is likely to lie at somewhere between 2 and 4 hours. Abnormal endothelial function also allows increased cellular migration and promotion of atherosclerosis and persists for longer than the observed changes in haemodynamics. Yeung et al correlated abnormal coronary vasoconstriction to mental stress in atherosclerotic coronary arteries to a failure in endothelial function as assessed by acetyl choline infusion and also to haemodynamic stress reactivity, and so coronary

vasoconstriction may also play a part in the pathogenesis of stress induced ACS [508]. Kop et al also demonstrated that atherosclerotic coronary constriction was more frequent in more psychophysiologically reactive individuals [509].

Similarly the potentially harmful effect on platelet aggregability persists at 2 hours post stress with no clear sign of recovery. The true length of this effect may last for several hours, thus placing patients at increased risk from ACS at a time after a stressful stimulus. It is interesting that there was an increased risk for emotional stimuli for ACS at 2 hours post stimulus but only in the one hour post exercise, and the triggering pathophysiology of these two stimuli may be different. The platelet effect may be important not only for intravascular coagulation but for inflammation and possible plaque rupture (see Chapter 9 for discussion)

The link between social class and haemodynamic stress responses has previously been demonstrated by Steptoe et al [147 178 587]. This study used a composite index of social deprivation and showed greater SBP responses in the most deprived patients. There is well documented link between social factors and the incidence of CAD and of acute cardiac events (see Chapter 3). This provides additional evidence to support an underlying difference in the dynamic pathophysiological responses to stress as being a potential mediator in this social gradient. Also the recovery rate was inversely proportional to social deprivation and so deprived patients not only have more severe haemodynamic responses to stress but also more prolonged responses. This may contribute to an increase in cumulative harmful haemodynamic effects.

It is not clear why educational achievement (and not deprivation index) should predict the platelet response to stress as both are surrogates of social position. This may be a

reflection of the small sample size. Thus, it is likely that social position also influences CAD and specifically the risk of external psychosocial triggers acting as precipitants of ACS by platelet effect as well as haemodynamics. This effect of social influences upon psychosocially triggered AMI has previously been demonstrated by Mittleman et al [312], who found that educational achievement moderated the effect of anger as an acute trigger, a finding replicated in the ACCENT study (Chapter 8).

The finding that patients with emotional triggers of ACS have an exaggerated platelet response to stress compared with non-triggered ACS controls suggests a major role for the platelet in post plaque rupture thrombosis as part of the ACS pathogenesis. As discussed previously, the inflammatory associations of platelet activation may also contribute, but it seems likely that the major effect is in intravascular coagulation. As discussed in chapter 2, autopsy findings have revealed many plaque ruptures that have remained clinically quiescent [16]. It may be that a significant part of the transition from emotional triggering to clinical ACS is not merely in plaque rupture but in the pro-coagulative response that follows. This study shows that the exposure to an emotional trigger heightens this response. This also ties in with the clinical finding in chapter 8 that anger as an emotional trigger increases the odds ratio of STEMI compared with NSTEMI, and the mechanism underlying this may well be more complete vessel occlusion secondary to increased thrombosis.

It is probable that both haemodynamic and haematological factors work in concert in the production of ACS. Other factors such as inflammation and arterial spasm are likely to play a part as well. It may also be that people differ in the contributions of these pathophysiological mechanisms to the pathogenesis of their ACS. It is interesting that the peak haemodynamic response to stress is relatively short-lived whereas the platelet

aggregability is more persistently elevated. These two factors may be relevant in the timing of ACS post stress trigger. Some people may have a haemodynamic stimulus for plaque rupture and may present soon after the trigger stimulus, others may have no initial symptoms but present later due to the effect of platelet aggregability on what would have otherwise been a silent plaque rupture. Alternatively, they may present later because of inflammatory effects of the stressful stimulus leading to acute inflammation and plaque degradation and subsequent rupture. Both emotional triggering and educational achievement were linked to heightened platelet activation to stress. In the ACCENT study, it is notable that there was a tendency for anger to act as a trigger of ACS in less educated patients. Educational achievement may modify the physiological responses to psychological stress, although there was no difference seen in the self-reported perception of induced stress in this study.

The stress tasks that were used in this study were different to those used in Chapter 9. The reason behind this is that the largest laboratory studies of psychological reactivity in patients with CAD, the PIMI study [482] used the Stroop / Speech combination, and so the same combination was used to allow comparison with these earlier investigations. This combination was not used in Chapter 9, as the purpose of that study was to compare CAD patients with normal volunteers and to specifically analyse the link with social class (data published elsewhere[579]). The Stroop / mirror trace combination had been used in most of the previously published work in this area and so was used again for uniformity and comparability. The CAD patients used in Chapter 9 were more varied than those in the ACCENT study in that they included post ACS patients and also patients who had presented with stable angina, never having sustained an ACS. Consequently a comparison between the two groups would have been difficult.

Strengths of this Study

The strengths of this study include the fact that it is the first work of its kind specifically to analyse psychophysiological reactivity in patients post-ACS, and to correlate this with clinical findings concerning triggering. We were therefore able to link the clinical experience of emotional triggering with likely psychophysiological mechanisms. Although preliminary, the study has supported the main hypothesis, producing statistically significant data that reinforce the theoretical link between psychosocial trigger factors and pathophysiological mechanisms implicated in the triggering of ACS. A further strength is the fact that the majority of the patients were studied in a drug free state and that all patients were studied free from the effects of aspirin and statins. Additionally, investigators were blinded to the trigger status of laboratory patients.

Weaknesses of this Study

The primary weakness of this study is the small number of patients who consented to take part in laboratory testing. As discussed earlier, this was predominantly due to exclusion criteria designed to maximise patient safety. However a large number of people who were suitable declined to take part in the study, so important selection factors must have been operating. The study is also weakened by the fact that only white males were tested. This was not due to selection bias on the part of the investigators but that no non-whites or women consented to come for testing. Women were older than men in the ACCENT sample, and were more likely to have co-morbid factors preventing study. The population for this laboratory study was also better educated than the ACCENT population overall, and so care must be taken in extrapolating the results found here into other population groups. A subjective observation was that similar to other studies recruiting volunteers, our participants were very motivated to help in research and so some self-selection bias was probably operating. These patients may differ from those

unwilling or unable to participate in unmeasured characteristics. Another limitation of the study is that because of Ethics Committee requirements we were required to study a small number of patients (5 patients) on beta-blockers. This number was too small to make any meaningful statistical comparison regarding the benefits of beta-blocking drugs. The issue of chronic medication is obviously important. This has been considered in the "discussions" section of Chapter 9. It is interesting that there is a prolonged abnormality of both haemodynamics and platelet function lasting for at least 2 hours after brief acute mental stress. It would be enlightening, although difficult, to quantify this length of time more accurately under laboratory conditions. The study performed here involved patients attending the department at 09.00 on the day of testing for preliminary interview before aiming for a 09.30 start in the laboratory. The usual finish time was around 12.30. It would be inconvenient and uncomfortable for patients to be instrumented for a longer period of time without eating, using the toilet or being able to walk around.

Further studies

It is essential to increase the sample number in this study both of unmedicated patients but also of patients on beta-blockers, not only to increase the statistical power of the study, but also to examine the effect of antagonising sympathetic nervous system stimulation. It will also be interesting to assess the effects of acute stress on markers of inflammation in this population. These will be assayed from frozen samples at a later date, and the results are outside the remit of this thesis. Other studies that would be interesting would be to compare vascular endothelial function in trigger versus non-trigger groups and also, in work analogous to that performed by Kop et al, Boltwood et al and Yeung et al), to examine the effects of acute mental stress on coronary vascular tone [508 509 512].

Tables

Table 10.1 Patients excluded from the study

Reason excluded	Number
Declined but suitable	48
Hypertension	50
Dead	5
Lives too far away	12
Lost to follow up	14
New co-morbidity / limiting co-morbidity	23
Persistent symptoms	18
New anxiety or depression	6
Poor LV function	3
Night worker	2
Blind	1
Agreed (pending study)	2
Within 6 months of ACS or revascularisation	59
Studied	20
Total	263

Table 10.2. Demographics of the Trigger study population

Age at time of testing		56.05 (± 8.31) years
Time from ACS to lab testing (mean)		15.6 months
Body Mass Index		29.50 (± 3.98)
Waist-hip ratio		1.01
Male		20 (100%)
White		20 (100%)
Education	None	7 (35.0%)
	Up to O level	5 (25.0%)
	A level and above	8 (40.0%)
Deprivation index	0	12 (60.0%)
	1	4 (20.0%)
	2	4 (20.0%)
Smoking status	Never smoked	4 (20.0%)
	Ex – smoker	6 (30.0%)
	Current or recent smoker	10 (50.0%)
ACS type	NSTEMI / UA	7 (35.0%)
	STEMI	13 (65.0%)
Previous MI	No	20 (100.0%)
	Yes	0 (0%)
Heart Failure	No	20 (100%)
Stress as ACS trigger	Yes	3 (15%)
	No	17 (85%)
Anger as ACS trigger	Yes	2 (10%)
	No	18 (90%)
Depression as ACS trigger	Yes	4 (20%)
	No	16 (80%)
Any emotion as ACS trigger	Yes	7 (35%)
	No	13 (65%)

Table 10.3 Physiological Stress Responses – Haemodynamic Stress responses

	Baseline	Stroop	Speech	Recovery 25-30 mins	Recovery 70-75 mins	Recovery 115-120 mins
SBP (mmHg)	122.2 ± 14.1[a]	153.7 ± 22.5[b]	159.6 ± 21.8[c]	137.5 ± 14.0[d]	138.7 ± 14.6[d]	134.9 ± 17.3[d] *
DBP (mmHg)	76.3 ± 10.3[a]	92.5 ± 12.0[b]	93.3 ± 14.2[b]	85.5 ± 10.8[c]	87.1 ± 10.5[c]	84.5 ± 12.9[c]*
Heart Rate (bpm)	64.8± [a]	71.5 ± [b]	76.7 ± [c]	63.4 ± [a]	63.1 ± [a]	61.6 ± [d] *
Stroke Volume index	53.8 ± 8.5[a]	51.0 ± 6.1[a]	53.3 ± 10.8[a]	50.5± 7.1[a]	49.2 ± 10.5[a]	51.1 ± 12.6[a]
TPR	0.65 ± 0.13[a]	0.80 ± 0.18[b]	0.75 ± 0.15[b]	0.82 ± 0.15[b]	0.89 ± 0.27[c]	0.85 ± 0.25[c] *

TPR = total peripheral resistance

- * = p = < 0.001 within subjects effects

Values with the same superscripts [a,b,c] etc are not significantly different from one another, but that those which have different superscripts are significantly different.

Table 10.4 Physiological Stress Responses – Platelet Stress responses

	Baseline	Post-Task	30 mins post	75 mins post	120 mins post
Total PLA	5.28 ± 1.04 [a]	5.96 ± 1.42 [b]	6.03 ± 1.34 [b]	6.06 ± 1.25 [b]	6.17 ± 1.19 [b] *
PL - mono	7.72 ± 2.07 [a]	9.60 ± 4.10 [b]	9.67 ± 4.28 [b]	9.68 ± 4.23 [b]	8.78 ± 3.67 [a]
PL - neut	4.84 ± 1.04 [a]	5.58 ± 1.50 [b]	5.60 ± 1.44 [b]	5.66 ± 1.28 [b]	5.80 ± 1.24 [b] *
PL – lymph	4.29 ± 1.06 [a]	4.77 ± 1.07 [b]	4.81 ± 1.04 [b]	4.75 ± 1.03 [b]	4.99 ± 1.06 [b] *

- * = p = < 0.01 within subjects effects

Values with the same superscripts [a,b,c] etc are not significantly different from one another, but that those which have different superscripts are significantly different.

Figures

Figure 10.1 Systolic and diastolic blood pressure responses to stress (all patients)

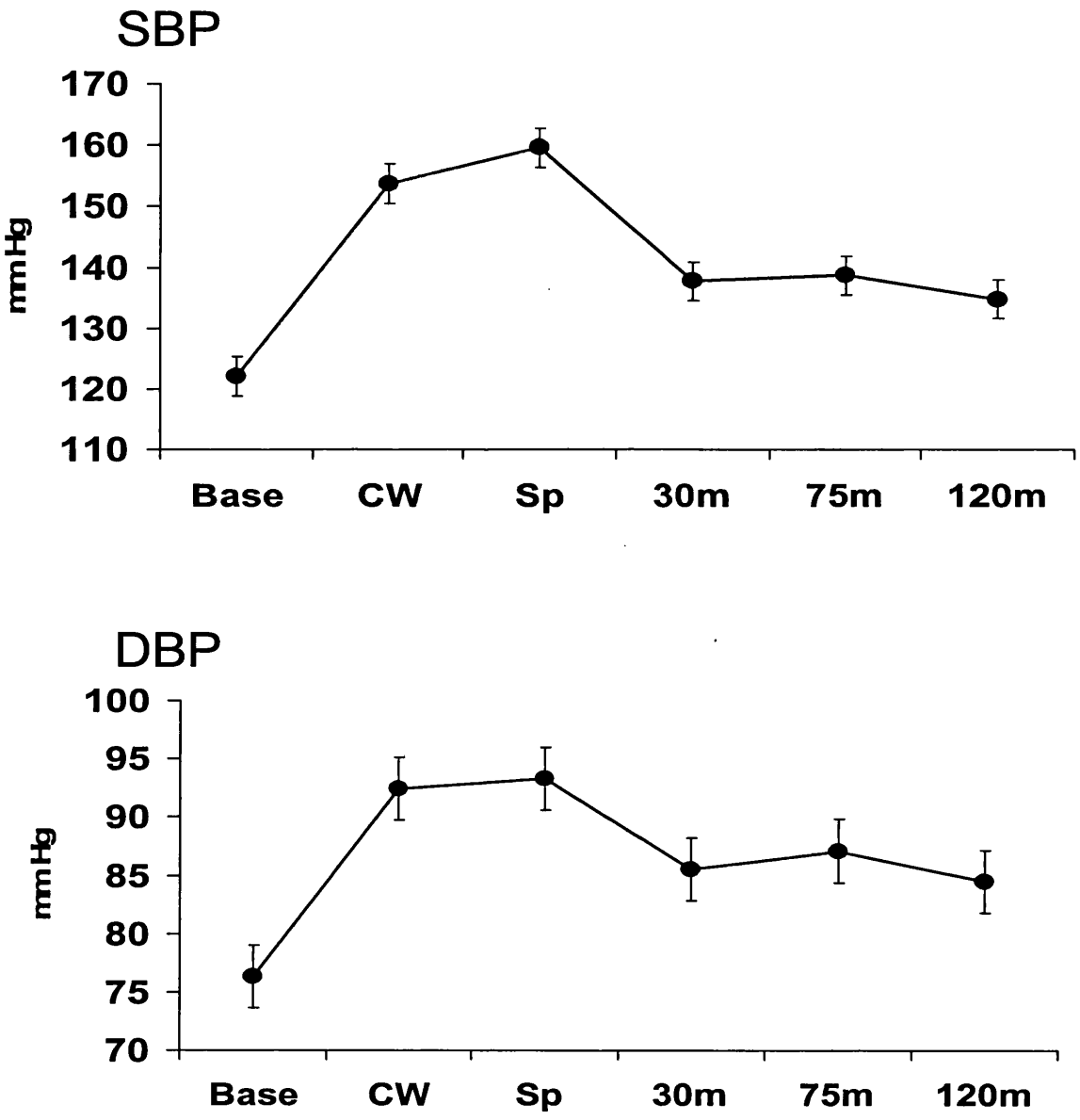


Figure 10.2 Cardiac Output Index (COi) and Total Peripheral Resistance (TPR) responses to stress (all patients).

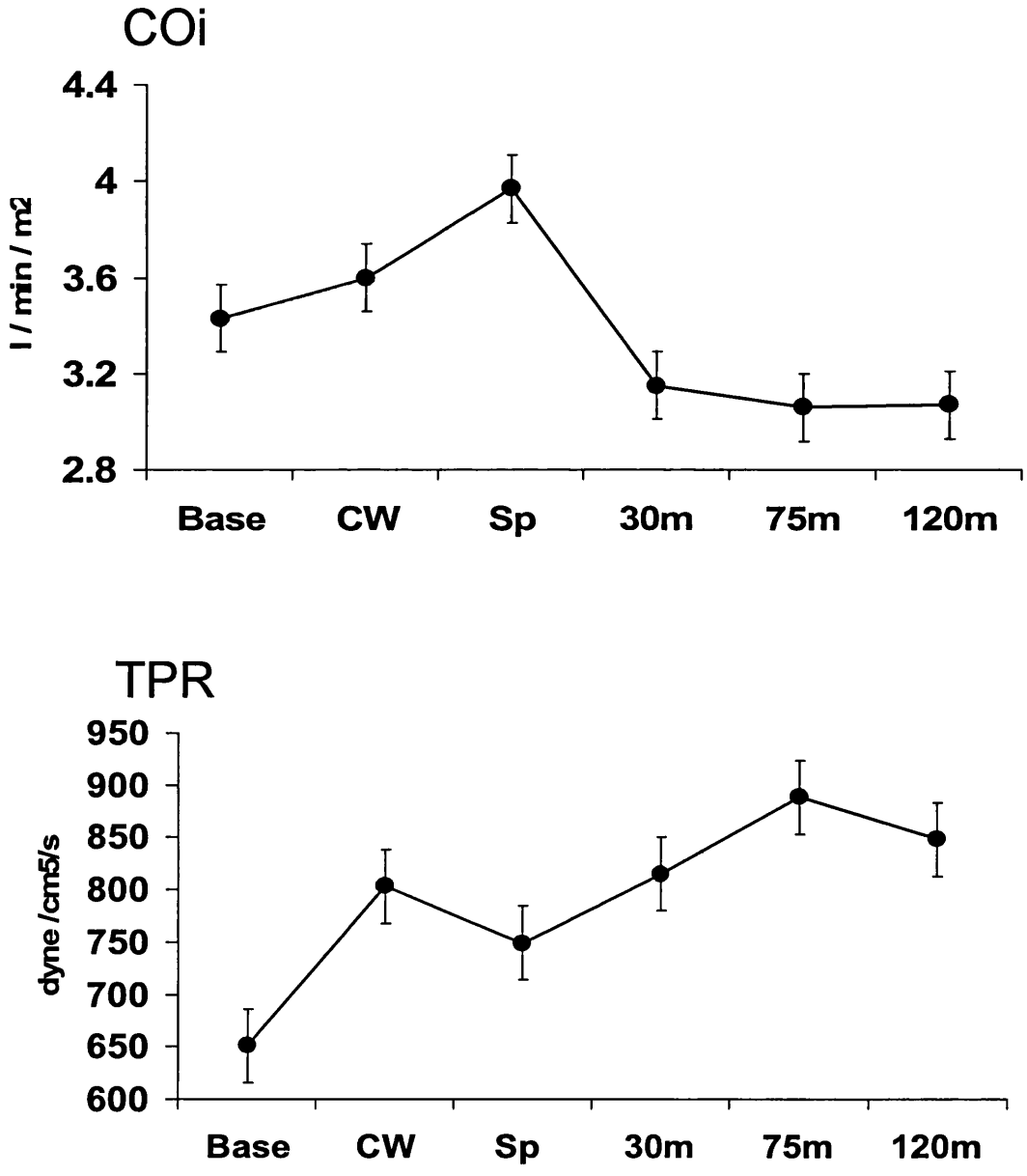


Figure 10.3. Heart Rate (HR) and Stroke Volume Index (SVi) Responses to Stress (all patients).

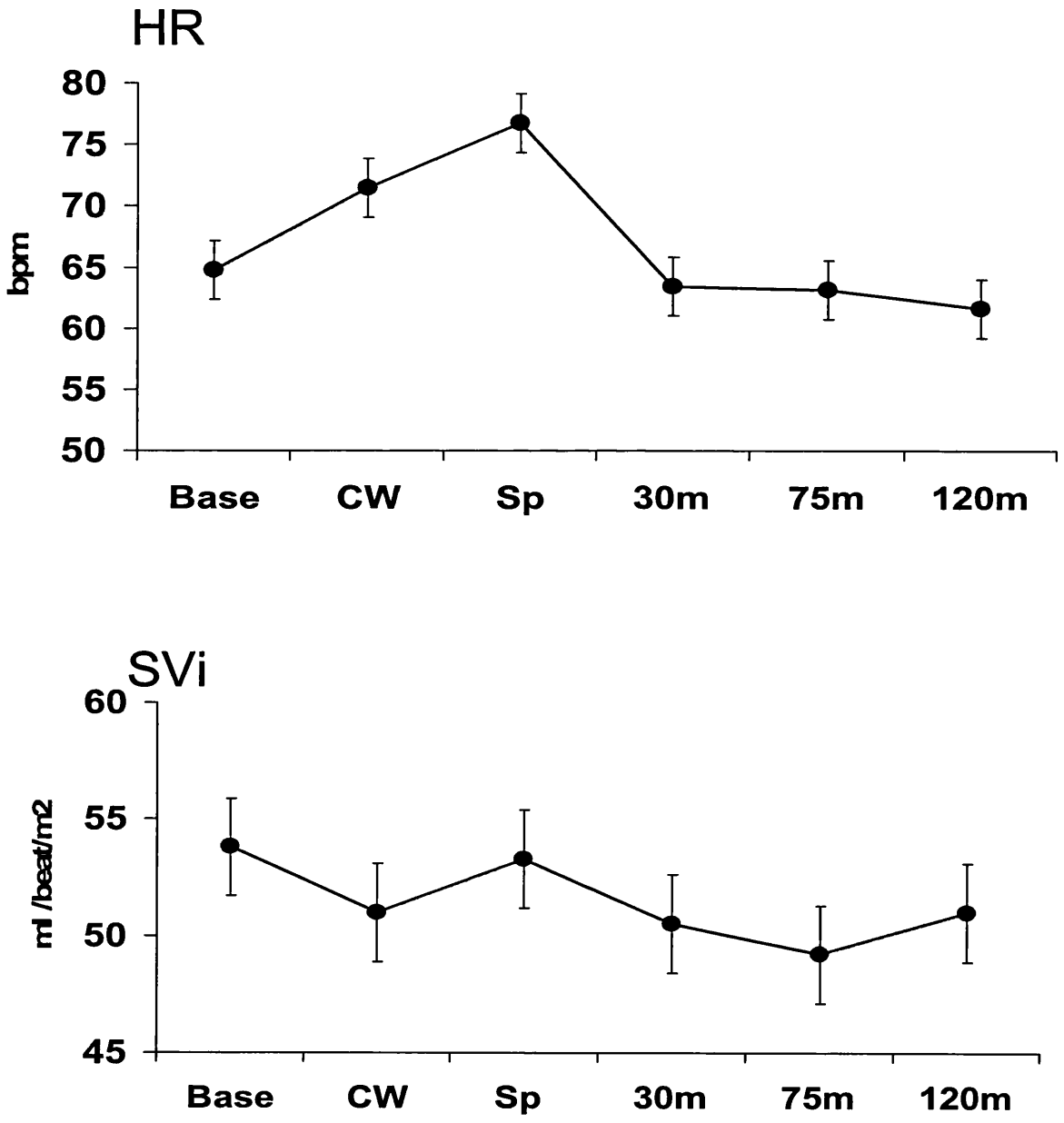


Figure 10.4. Total PLA Responses to Stress (total and PL – monocyte aggregates) (all patients).

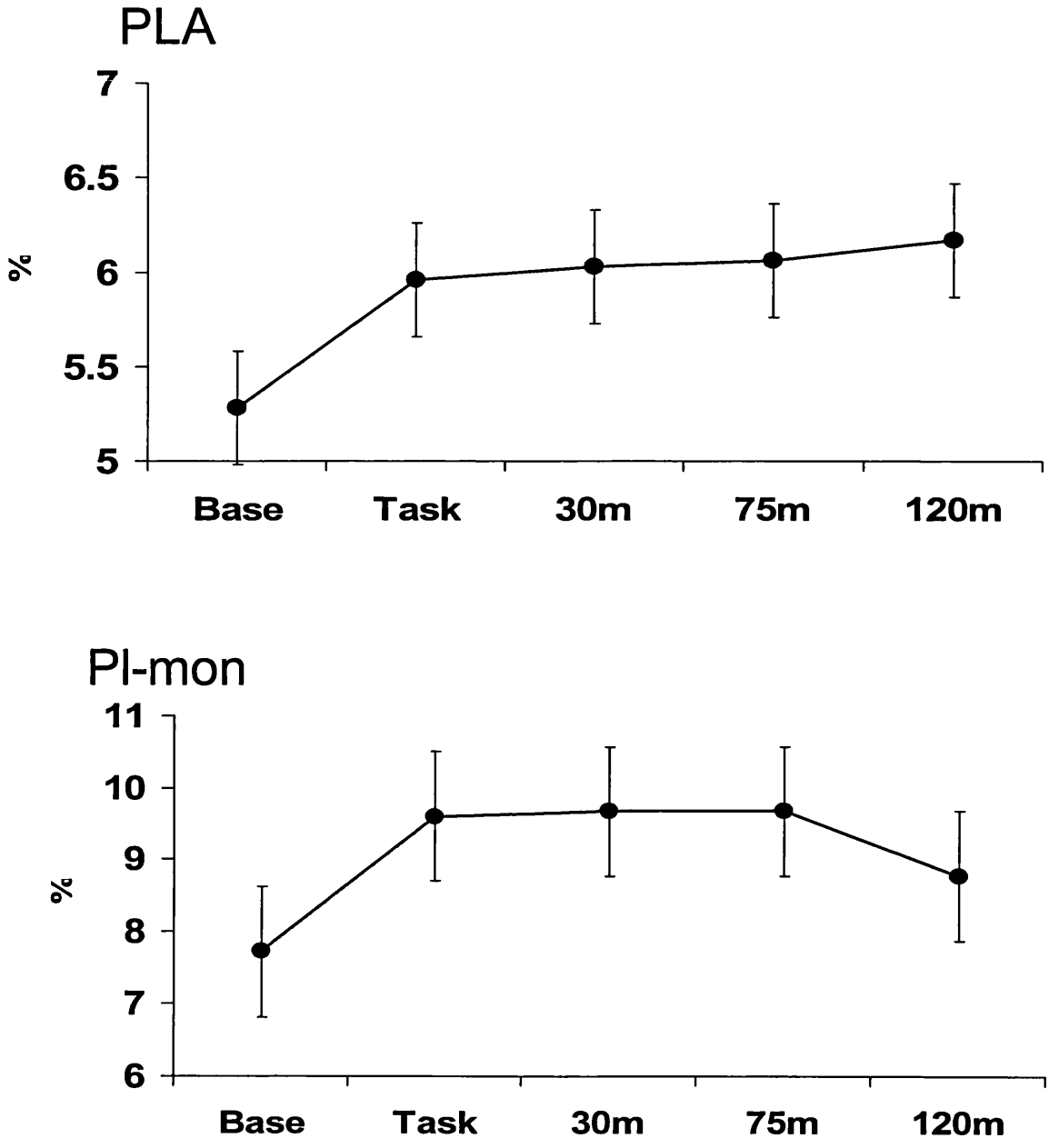
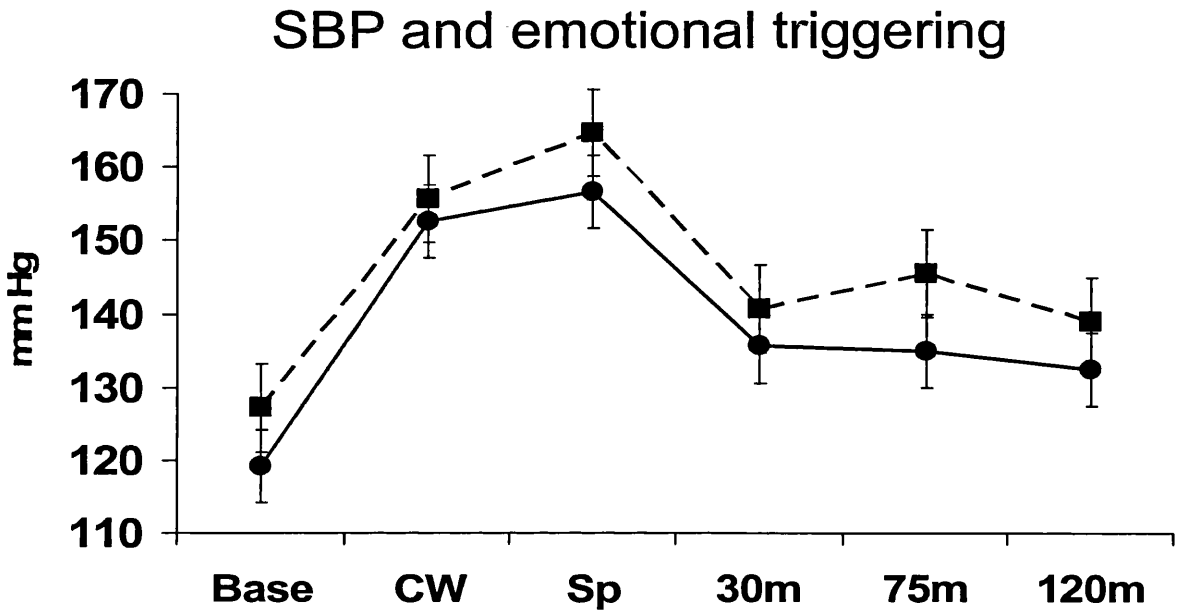


Figure 10.5 Emotional Triggering and Systolic Blood Pressure (SBP) and Cardiac Index. Trigger versus non-Trigger Group (Broken line = Trigger Patients. Continuous line = non-Trigger Patients)



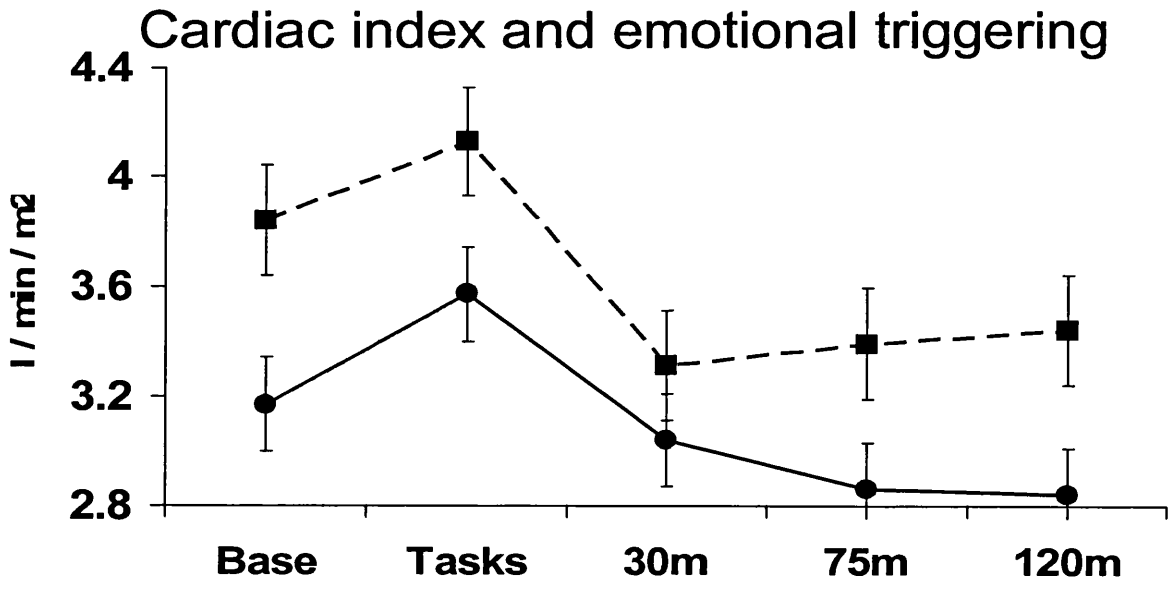
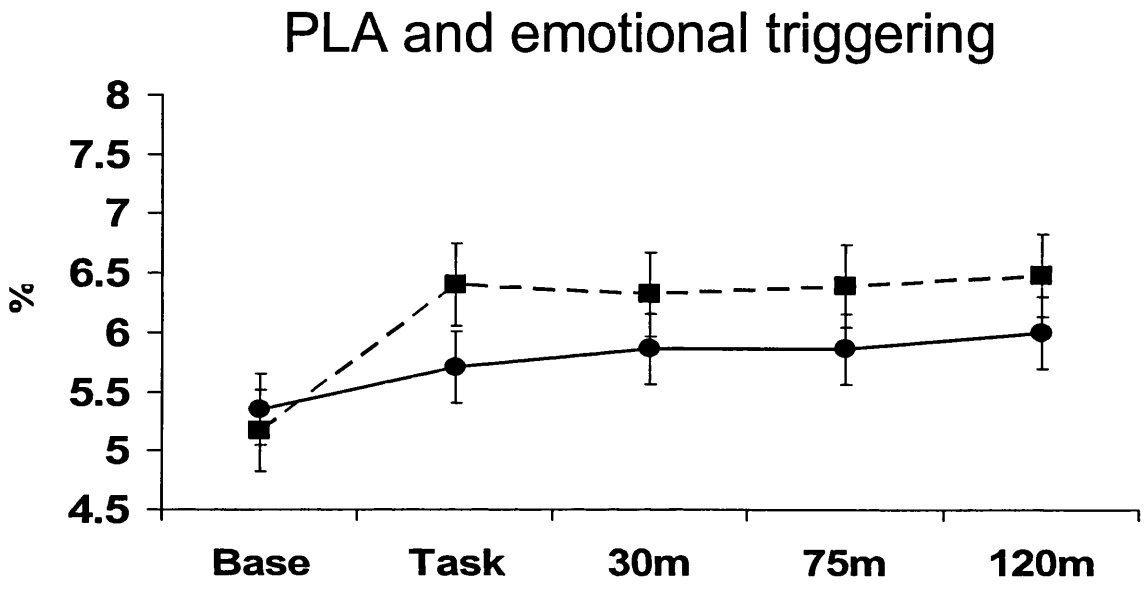
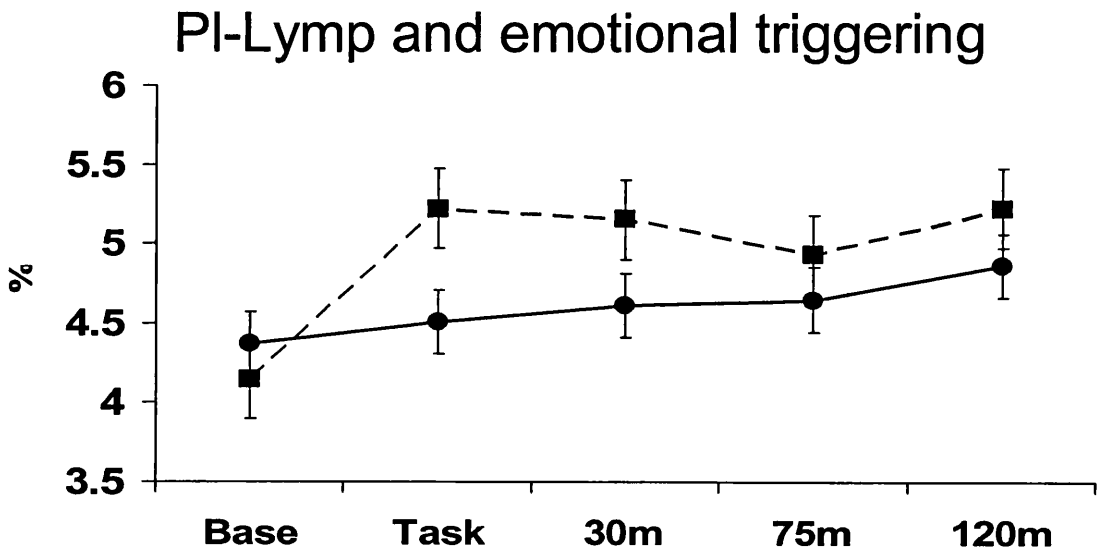


Figure 10.6. Variation in Total PLA and PLA - Lymphocyte Responses to Stress, Trigger versus non-Trigger Group. Broken line = Trigger Patients. Continuous line = Non-Trigger





Chapter Eleven

SUMMARY AND DISCUSSIONS

11.1 SUMMARY OF FINDINGS

In this thesis, I have attempted to systematically appraise the current body of knowledge on the role of psychosocial triggers of acute coronary syndromes. Furthermore, I have added to it by identifying gaps in this knowledge and conducting original new research. Data on previously identified risk factors have been reinforced, new risk factors for ACS onset identified, and new interactions and potential pathways to disease revealed. The thesis has identified a complex integration between social, psychological, clinical and biological factors.

Each chapter of this thesis finishes with a discussion about the issues raised therein and about the clinical findings and implications. Consequently, this final discussions section will include a summary and broad overview of the issues raised rather than going into specific details in depth once more. I also address the limitations of the work, and implications for future research. In the early chapters, I have reviewed the processes by which coronary arterial atheroma develops and progresses to form atherosclerotic plaques. I have also examined the literature regarding the factors involved in the development of plaque vulnerability and subsequent plaque rupture with its possible clinical and non-clinical sequelae, and how this is relevant in the study of triggers.

Specifically, the role of psychosocial factors in atherogenesis has been discussed, and socio-economic class, depression, social isolation, and chronic stress emerge as being

strongly implicated as stimulating atherosclerosis and clinical events. A small but growing literature also suggests that anger promotes atherogenesis, but work done on hostility is inconclusive. It is also apparent that the initiation of ACS is not a completely random event and is influenced by internal physiological rhythms, temporal (daily, weekly and seasonal) patterns and the experience of external trigger factors. Some external trigger factors had been subject to analysis previously, especially physical exertion, but for the majority of other implicated factors the evidence was absent or very limited. This thesis has provided further in-depth examination of these trigger factors.

The way in which these psychosocial factors can then act as trigger factors to mediate the rupture of a stable atherosclerotic plaque and cause a resultant clinical syndrome has also been scrutinized (Chapter 5). The physiological mechanisms that may underpin this translation of a trigger factor into a measurable clinical end-point have been closely examined and discussed. Similarly, current data on mental stress induced myocardial ischaemia has been comprehensively and systematically reviewed (Chapter 6). These reviews have been published in the European Heart Journal and other journals [26 282 319 438].

11.1.1 New Findings

What was also unclear previously was how external psychosocial triggers interacted with the social environment as well as intrinsic physiological factors to influence not only the occurrence of ACS, but also its clinical picture. It is worth re-examining the original aims of this thesis to see to what extent those objectives have been achieved.

Aim 1. To assess the prevalence of acute psychosocial factors triggering ACS.

The ACCENT study (Chapter 7) has shown roles for several behaviours as precipitants of ACS. These data strengthen the evidence already in existence for anger and physical exertion, but add to the literature by identifying previously unidentified roles for acute mental stress and depressive symptoms as triggers of ACS. The relative risk of ACS occurring within an hour of unaccustomed exertion was 4.75 (95% confidence interval 1.58 to 19.2), and the relative risk of ACS occurring within two hours of experience of anger was 2.00 (95% confidence interval 1.04 to 4.00). These data correspond with and reinforce existing data in this area. Experience of depressive symptoms gave a two-fold increase in the risk of subsequent ACS (2.22, 95% confidence interval = 0.97 to 5.54) and acute mental stress an almost three-fold increase in relative risk (2.71, 95% confidence interval = 1.44 to 5.42). These are new findings. No controlled study has previously shown acute depressive symptoms or acute experience of mental stress to result in ACS onset.

Aim 2. To examine the association between acute psychosocial triggers and clinical parameters

Other important new findings include the identification of the link between social deprivation and the risk of anger acting as an ACS trigger independent of gender, age and ethnicity. A threefold increase in risk of anger-triggered ACS was observed comparing the most deprived tertile with the least deprived revealing a high-risk population. This demonstrates the complicated interface between social, psychological and clinical factors. As discussed in Chapter 3, there are many potential mechanisms by which living in socially deprived conditions might influence CAD. This social

modification of ACS triggering adds to the debate about health inequalities and social healthcare policy.

The influence of psychosocial triggers are themselves affected by diurnal circadian rhythms and by the construct of the working week. This suggests modification by not only the body's intrinsic physiological variation but also by the social and mental stress of the working environment. Both anger and depressive symptoms were more common to act as triggers on workdays ($p = 0.001$ for depression, $p = 0.036$ for anger) compared with weekend days. Depressive symptoms were also more likely to act as triggers in the morning suggesting interaction with the body's own diurnal variation.

One of the most interesting findings is the increased likelihood of sustaining STEMI after triggering by the experience of anger. This suggests an effect of anger upon the physiology of vessel occlusion, and may reflect either more severe plaque disruption, increased coagulability, or coronary arterial spasm leading to flow diminution. It should be noted that although there was an increase in the incidence of ST elevation after an anger trigger, this did not translate into worse infarction as measured by the surrogates of Q-waves, troponin T or CK release, or subsequent development of heart failure. This is not the case with physical exertion, where there is more likely to be an ST elevation Q-wave myocardial infarction. This suggests that anger may have a transient influence on physiology and implicates a possible role in vascular spasm, in-keeping with previous research [512]. Finally one of the worrying findings of the ACCENT study was a gender bias discriminating against women in the invasive investigation of ACS. The majority of patients underwent PTCA, but a higher proportion of women than men were managed medically, as has previously been described in the literature [618]. This finding will be fed back to the participating cardiology departments for further investigation.

Aim 3. To examine whether patients with CAD have an altered psychobiological reactivity compared with healthy controls.

The two laboratory studies have focused on the interaction between psychosocial parameters and the haemodynamic and platelet responses to acute mental stress. The first laboratory study has shown that compared to healthy volunteers, CAD patients display exaggerated haemodynamic reactivity to acute mental stress and an abnormal pattern of platelet activity, both of which could be implicit in the development of both acute and chronic CAD. The platelet response is equal in the two groups immediately after stress, but platelet aggregability continues to rise at 75 minutes post stress in the CAD patients whereas it has returned to pre-stress levels in healthy controls. This platelet response still remains significantly abnormal at 120 minutes post stress in the post ACS group in the second laboratory study (Chapter 10). Furthermore there could be a link between the platelet activation and the inflammatory response to mental stress in CAD patients, as suggested by the finding that stress induced increases in CRP were proportional to the increases in PLAs in CAD patients ($r = 0.68$, $p < 0.05$) but not in controls, after adjusting for income, body mass index, and waist/hip ratio (Chapter 9).

Aim 4. To examine whether patients with ACS triggered by acute psychosocial factors have an altered psychobiological reactivity compared with non-triggered ACS patients.

Preliminary data from the second laboratory study confirm the pattern of haemodynamic and platelet responses to acute mental stress in patients who have sustained ACS. It shows that the pattern is similar to that shown in the first laboratory study in patients with stable CAD but also that the abnormal platelet response still persists at two hours

post mental stress. It must be remembered that although this is only a small study, it has nevertheless had the power to provide statistically significant and plausible data.

This study yet again shows the important interaction between factors in the social environment and the psychophysiological stress response. The study also indicates the possibility that social factors may place individuals at a higher risk of ACS being triggered by external or by psychological stimuli. For example, the extent of haemodynamic psychophysiological reactivity is proportional to the level of deprivation (B = 10.5, 95% confidence interval = 0.14 to 20.9, p = 0.047) and platelet reactivity inversely proportional to educational achievement (independent of baseline PLA, age, BMI, waist-hip ratio and smoking, B = - 0.74, 95% confidence interval = -1.20 to -0.29, p = 0.004). Individuals with psychosocially triggered ACS differ from those in whom there is no apparent ACS triggering. In patients who have had ACS precipitated by external trigger factors, there is greater cardiac output response to stress (F = 7.29, p = 0.018) and slower haemodynamic recovery in the trigger group. Similarly, platelet stress response is significantly greater in the emotional trigger group than the non-trigger group after controlling for baseline PLA, age, BMI and smoking (F = 4.91, p= 0.045).

11.2 LIMITATIONS OF THIS THESIS

The research studies presented in this thesis have several limitations, most of which are discussed at the end of each chapter as appropriate. The ACCENT study has looked at a very tightly defined population and care must be taken in the extrapolation of these data to other populations. The study population is almost all based in urban South-East England, is mostly male and includes relatively few non-white patients. There is a high incidence of financial and social deprivation and a relatively low level of education. The

patients are all English speakers and results may not apply to non-English speaking groups. Because of the strict exclusion criteria the population are quite young, lack any significant co-morbid illnesses and are thus a selected group. It is important to bear in mind that although this population had minimal confounding factors, they are very different from the more elderly, multi-cultural population with multiple other pathologies who present acutely with ACS.

There has quite clearly been a selection bias in the recruitment of patients which has been intentional, but there may have been further selection biases on the parts of the recruiters. There could have conceivably been bias in the way that data were recorded and there could have been conscious or sub-conscious bias amongst the interviewers to make patients accounts or investigative results tie in with the pre-study hypotheses. Another limitation is the fact that it was not possible to attempt to recruit all ACS admissions into the study or to keep accurate registry data.

The study is by necessity retrospective and is thus prone to many potential errors and biases. Because of the time taken from ACS to interview then there may have been some memory decay during that time. Patients' accounts of events are also prone to bias due to their own personal health beliefs, illness attributions and potentially the wish to blame either other people or circumstances for their illness. Actual presentation to health care services with ACS may also be subject to the beliefs and influences and there may be patients who do not present to hospital which would bias the study population.

It is also possible that the emotional symptoms were a response to cardiac disease rather than a causative factor. It is known that even a mild inflammatory stimulus produces a measurable change in mood [464] and it is possible that the physiological response to

inflammation in the coronary tree is sufficient to foster psychological symptoms in some patients. Thus, it was not possible incontrovertibly to establish a causal link between psychological states and ACS.

Although the ACCENT study has had enough participants to show the effects discussed, it is unfortunately not large enough to provide any meaningful data on adverse cardiac events or outcome. This would require a much larger prospective clinical epidemiological study. One of the other problems is that recruitment was not as brisk as had been hoped. As discussed in Chapter 8, there were a considerable percentage of patients classified on admission as suffering from an ACS who were not suitable for recruitment. With a greater number of participants, the data may well have shown stronger effects for the already statistically significant data that have been presented, as well as possibly identifying significant effects for some of the stronger trends seen such as the relationship between depressive symptoms and ACS onset. Similarly, as the laboratory study presented in Chapter 10 used the ACCENT patients as its recruitment pool, a larger number of patients in the ACCENT study might have translated to larger numbers and more powerful data in that study as well. Ongoing recruitment to this study as discussed in Chapter 10 will hopefully address this issue. Also the same considerations regarding bias apply to these laboratory studies as discussed above and in Chapter 8 regarding the ACCENT study.

The structured interview used to obtain trigger data in the ACCENT study was based on the methods developed in the Onset and SHEEP studies of triggering. It should be emphasised that the same limitations apply to our methods as were pointed out in Chapter 5 for the previous work. Although a systematic approach was used and appropriate control data collected, the findings ultimately rely on retrospective patient

reports which are subject to many sources of bias. A valuable extension of this work would be to collect data from bystanders to corroborate patients' reports about their activities during the hours preceding symptom onset.

Both laboratory studies would have benefited from larger participant numbers, but again this was partly limited by the necessity for rigorous exclusion criteria and the minimization of potential confounding factors. Because of restrictions imposed by local ethics committees, the medication status of the patients was variable as has been described in detail. This has been handled by statistical correction, but this approach is not ideal. Similarly the participants in both of the laboratory studies are male, relatively young compared with the population presenting with ACS, and almost exclusively white. They are English speaking and more educated than the general ACS population. All laboratory participants were volunteers and it is likely that those patients who volunteered to take part in this further research were different from those who refused. There is ample evidence to suggest that volunteer populations differ from the population at large. For example, in the Whitehall II epidemiological study, initial recruitment to the sample ranged from 81% in high status to 68% in lower status groups (Marmot et al, 1991). It is possible in both of these studies that chronic medication may have played some role in alteration of physiological variables. The duration of withdrawal from aspirin, statins and beta-blockers should have been adequate, but there would have been a possible small effect still from tissue soluble ACE inhibitors such as ramipril.

11.3 STRENGTHS OF THIS THESIS

The research presented in this thesis has demonstrated interesting interactions between psychology, social factors and physiology leading to increase in clinically important

cardiac events. These wide-ranging interactions have not been studied before in ACS patients. New associations have been revealed and understanding of underlying mechanisms reinforced. The studies have all had sufficient statistical power to demonstrate significant results. The literature reviews and new data have been of sufficient strength that to date the work presented in this thesis has already resulted in six publications in peer reviewed journals [26 282 319 438 550 619] with hopefully more to follow.

The use of the case-crossover design in the ACCENT study has allowed controlled data to be obtained and there have been minimal confounding factors. Most studies of triggers are observational and lack control data. Patients were interviewed an average of 2.5 days after admission, much sooner than in other work in this area, hopefully leading to more accurate data recall.

11.4 CLINICAL IMPLICATIONS

At this early stage of research into psychosocial factors and acute coronary syndromes the immediate and direct clinical implications are few, but the future possibilities are potentially massive. The clinical implications of the work presented here potentially lie in each of the several stages of the process from atherogenesis to ACS, and it may be possible to intervene upon on these to reduce psychosocially mediated cardiac events. I have identified high-risk groups for psychosocially mediated cardiovascular disease and ACS, and it may be possible to target therapies to those at the greatest risk of future events. Further epidemiological, psychological, laboratory and intervention studies will be required to define culpable mechanisms and identify treatments. Public health and social policy changes could theoretically reduce risk by improving the social and working environment and reducing adverse psychosocial exposures. Persons with depression or high trait anger could be identified and receive pharmacological or

behavioural therapy to reduce this, and receive information about exposure avoidance to decrease the incidence of psychologically mediated triggering. Other pharmacological treatments may be relevant. For example, if coronary arterial spasm is found to play an important role in the pathogenesis of externally triggered ACS, then acute therapy with calcium channel blockers or combined alpha and beta-adrenergic antagonists may be beneficial. Further work on post ACS populations may also reveal a benefit with carefully focused CBT and/or antidepressant treatment along the lines of the SADHART and ENRICHD studies [207] [226] as discussed in Chapter 3.

Apart from ongoing public-health policy intended at health promotion and removing health inequalities, it would be otherwise difficult to attempt any form of CBT or pharmacological therapy as a preventative measure in primary care, and it would take an enormous prospective randomized controlled trial to prove the data to justify such a measure. Consequently it would seem more appropriate to use such measures as part of secondary prevention interventions, possibly in association with cardiac rehabilitation programmes or even by formulating a specific cardiac rehabilitation programme for these patients. It is premature to advocate therapeutic interventions based on the evidence presented here, but it is entirely feasible that further research as delineated above could provide these data.

11.5 IMPLICATIONS FOR FUTURE RESEARCH

11.5.1 Epidemiological Studies

As previously mentioned, the ideal study would be a large prospective study with greater statistical power to examine associations and assess mortality and adverse cardiac events.

This would have the power to examine less frequent exposures such as drug use and sexual intercourse as triggers, which this thesis was not powered to do.

11.5.2 Psychological Studies

Potentially more detailed psychometric profiling of anger triggered ACS patients might reveal more information about traits such as anger proneness or methods of coping with anger. More information is needed to detail the harmful component of the anger construct. It would be helpful to discover what typifies anger prone patients in an attempt to identify the group at highest risk of triggered cardiac events. A targeted counseling programme could then be initiated to try and reduce the intensity of experienced anger. Future analysis of the psychometric data collected from patients in all three studies will hopefully be informative .

11.5.3 Laboratory Studies

Further laboratory work will also be helpful in identifying the underlying mechanisms involved in emotionally and behaviourally triggered ACS. More studies along the lines of the experiment described in Chapter 10 could provide more information about the mechanism of triggering in emotionally induced ACS. Further patients for this study will be recruited, and will also hopefully provide the opportunity to assess the impact of medication such as beta-blockers, platelet inhibitors etc on the physiological stress responses in post ACS patients. This could then translate into suggestions for secondary prevention drug therapy. Also further work may identify serological parameters that are associated with increased risk of ACS which may allow prevention work to occur.

In this thesis, two potential culprit mechanisms (platelet and haemodynamic responses) have been focused upon. As discussed in Chapters 2 and 5, there are several other potential pathophysiological mechanisms which could be scrutinized in laboratory studies, such as IL-6, adhesion molecules and arterial tone which might possibly be illuminating.

Similarly, catheter lab studies could be performed on patients with anger induced ACS in a similar way to the study by Boltwood et al [512], to see if there is a difference in stress-induced coronary arterial spasm in patients with anger-induced ACS compared with controls. This could potentially have a therapeutic benefit. The predominant driving force to coronary artery spasm is unopposed alpha-adrenergic vasoconstriction. Consequently there may be a benefit in treating patients with anger-induced ACS with a combined alpha and beta-blocker such as labetalol, rather than a simple beta-blocker as is the case in current practice, or by using drugs such as calcium channel antagonists.

11.5.4 Intervention Studies

As discussed in Chapter 3, the role of pharmacological and behavioural therapy for psychosocial factors post ACS is as yet not clearly defined. Such a programme of therapy would need to be both cost effective and efficacious. For an intervention to be successful, it has to be targeted at the people who will gain most benefit from its effects, and identifying these high-risk populations would be an important goal of future research.

It might be possible to intervene at each step of the pathological pathway from initiation of atherosclerosis to ACS and then subsequent secondary prevention. This could take the form of social, behavioural or pharmacological therapy. However, much more data about the responsible mechanisms and the clinical implications are needed before a trial of drug treatment could be advocated.

Sub-group analysis from the ENRICHD study showed that CBT may be beneficial in a targeted population post MI [227]. The data from the ACCENT study are not conclusive but it suggests that possibly younger patients (for anger) and male patients (for depression) may have the most to gain. Interestingly it was male patients who showed the greatest benefit in the ENRICHD study [227]. This may reflect the possibilities that their psychosocial profiles and intrinsic methods of coping with adverse psychosocial events were more unfavourable to begin with, or that the CBT used was biased in favour of male patients. If a larger epidemiological study showed convincing evidence of depressive symptoms as triggers of ACS, then there may be an argument for a clinical trial with sertraline to assess outcomes and recurrent events in this population rather than for the more general post MI population used in the SADHART study[207].

11.6 ESTIMATE OF THE TRUE BURDEN OF PSYCHOSOCIAL TRIGGERING

Overall, 26.5% percent of our ACCENT study population were exposed to trigger factors only in the hazard period pre-ACS and 9.0% in the control period alone. This translates to an estimate of 17.5% of cases of ACS being due to psychosocial trigger factors. Using the old definition, there are at least 250 000 cases of MI in the UK per year.[2]. This translates to a figure of 43750 cases of triggered MI per year in the UK.

13.3% of patients experienced anger in the hazard period only and 6.7% experienced it in the control period only, This suggests that as many as 6.6% (13.3% - 6.7%) are due to the effects of anger as a trigger factor in ACS. This translates to a potential attributable risk of 16500 cases per year in the UK alone. If one examines acute stress then the results are greater, 18.8% - 6.2% = 12.6%, which translates to a population attributable risk of 31500 cases per year.

These figures are of course very crude and are likely to be overestimates of the true number because of the biases discussed above and in Chapter 8. However even if the true figure were only 1 or 2% then this still reflects a massive number of cases of ACS and cardiac death. Consequently the experience of these psychosocial triggers has an immense effect on the national and international burden of cardiovascular morbidity and mortality as well as for the consumption of healthcare and welfare costs.

11.7 CONCLUSIONS

Coronary artery disease cannot be viewed as a distinct clinical entity. Its initiation, progression and subsequent clinical manifestations are based on a complex interaction between genetics, intrinsic physiology, temporal influences, the social environment and the psychosocial risk factors discussed in this thesis. Psychosocial factors act at each step in the natural history of CAD, from the initiation of fatty streaks to plaque vulnerability and the triggering and clinical course of acute coronary syndromes.

Several pathophysiological mechanisms are implicated. Both haemodynamic and platelet function are likely to play an important role in the triggering of ACS and in the differences seen between the study populations in this thesis. These are likely to be

important in the translation of psychosocial experiences into coronary artery disease. It is however important to bear in mind that the difference elicited could be due to an occult physiological abnormality which could influence not only haemodynamic and platelet physiology but also be involved in the atherosclerotic process. Subsequent work on inflammation and endothelial function may be enlightening in this respect.

Recent epidemiological work calculated that the risk of psychosocial factors on a global scale is comparable with that of either hypertension or abdominal obesity [61]. When one considers the amount of media coverage and the treatment budgets that are spent on these two conditions, it seems clear that psychosocial risk factors in heart disease, although increasingly investigated, are still largely under-recognized and under treated in society leading to a huge global morbidity and mortality. The first step to addressing this imbalance is the identification of specific psychosocial risk factors, and then subsequently demonstrating the physiological mechanisms by which these risk factors precipitate cardiovascular disease.

Consequently, it is clear that the triggering of an ACS is a phenomenon far more complex than can be explained by physiology or plaque biology alone. There is a multi-faceted interaction between physiology, psychology, sociology, timing and behaviour that requires a broad and holistic view to appreciate. This will be essential in order to reduce future mortality from coronary artery disease.

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Appendices

ppendix i. ACCENT study patient information sheet

Royal Free and University College Medical School
UNIVERSITY COLLEGE LONDON

EPARTMENT OF EPIDEMIOLOGY AND PUBLIC HEALTH

Study of Emotional Factors and Quality of Life in Heart Disease

PATIENT INFORMATION SHEET (Confidential)

This research study is funded by the British Heart Foundation to try and explore how our emotions and behaviour influence the cardiovascular system in health and disease. The results of this study will help advance our knowledge of the links between the mind and the body. This exciting and important area of medical science will contribute to the understanding of heart disease, and aims to improve both the prevention and the treatment of this common illness. The study is being carried out by Professor Andrew Steptoe from the Department of Epidemiology and Public Health at University College London, in collaboration with Dr Jean McEwan from the Department of Clinical Cardiology. The researchers who will carry out the work are Dr Lena Brydon, Dr Sue Edwards and Dr Philip Strike.

Exactly what triggers heart attacks and unstable angina is unknown. We still don't know why people have a heart attack on one specific day and not on the day before or the day after. It is likely to represent a complex interaction of several factors. We are trying to find out whether lifestyle and emotional state make a contribution in some patients. We also want to learn more about how people respond emotionally to coming into hospital with a heart problem, and how these responses may relate to physical recovery and quality of life. We are particularly interested in linking the psychological factors with the underlying biology of heart disease, to see whether there are differences in the various chemicals in the blood that are involved in heart attacks and angina.

How You Can Help

We would like to interview you about what has been happening in your life over the last six months, right up until you came into hospital. This will take about one hour, and will take place on the Ward. We will also ask you to fill in some questionnaires in your own time. These concern how you are feeling about life, and how you cope with stress. When you were admitted to the Coronary Care Unit you had some blood taken. We would like to use some of that to carry out biochemical analyses for our research. We would also like to ask your permission to take a further 10ml sample of blood.

The second part of the study involves measurement of chemicals in saliva. We know that several hormones that affect the way the body works vary over the course of the day, and fortunately these can be measured in saliva. Several times over a day, we will ask you to put a cotton dental swab in your mouth for a couple of minutes, then return it to a storage tube. We would like to do this on one day while you are in hospital, and then again in a few weeks time after you have returned home. The samples you collect at home can be posted back to us (we will provide the postage and packing).

We want to emphasise that all results obtained will be strictly confidential and will only be used for medical research purposes. You will be free to withdraw from the study at any time without giving a reason. Taking part or deciding not to take part will not affect your medical treatment in any way.

Many thanks for reading this.

We hope you feel able to take part in our study, which will help us understand more about the causes of heart disease and how to manage it better.

Any questions to Dr. Philip Strike, Department of Epidemiology and Public Health, University College London, 1-19 Torrington Place, London, WC1E 6BT. Telephone 020 7679 1688

Appendix ii.

Royal Free and University College Medical School
UNIVERSITY COLLEGE LONDON

DEPARTMENT OF EPIDEMIOLOGY AND PUBLIC HEALTH

Gower Street Campus
1-19 Torrington Place
London WC1E 6BT

Study Number: 01/0156
Patient Identification Number for this trial:

CONSENT FORM (Confidential)

Title of project: **A Study of the Emotional and Behavioural Factors in Acute Coronary Syndromes**

Name of Researchers: Professor Andrew Steptoe, Dr. Lena Brydon, Dr. Sue Edwards, Dr. Philip Strike
Any questions to Dr. Philip Strike, Department of Epidemiology and Public Health, University College London, 1-19 Torrington Place, London, WC1E 6BT. Telephone 020 7679 1804

Please initial box

1. I confirm that I have read and understood the information sheet for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that sections of any of my medical notes may be looked at by regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐
4. I agree to take part in the above study. ☐

Name of patient	Date	Signature

Name of Person taking consent (if different from researcher)	Date	Signature
Researcher	Date	Signature

1 for Patient; 1 for Researcher; 1 to be kept with hospital notes

Appendix iii ACCENT study interview proforma

EMOTION Study: Structured Interview

Patient Study number:	Patient name:
Hospital no.	Date of Birth
Date and time of Admission:	Date & Time of blood sample:
Date of Interview:	Interviewer:
Outside temperature on date of cardiac event (from Met. office):	
Patient's address and phone number:	

Details Of Acute Coronary Syndrome

Admission BP	SBP:	DBP:
Admission pulse rate		
ST elevation?	Yes / No	If Yes, territory: Inf / Ant / Post / Lat / Inf-Lat / Ant-Lat / Post-Lat / not applicable
ST depression?	Yes / No	If Yes, territory: Inf / Ant / Post / Lat / Inf-Lat / Ant-Lat / Post-Lat / not applicable
T wave inversion?	Yes / No	If Yes, territory: Inf / Ant / Post / Lat / Inf-Lat / Ant-Lat / Post-Lat / not applicable
Bundle Branch Block?	Yes / No	
Arrhythmia?	Yes / No	If Yes, type: AF / VF / VT
Heart Failure?	Yes / No	
Aspirin?	Yes / No	
Heparin?	Yes / No	
Thrombolysis?	Yes / No unknown	If Yes, which thrombolytic? SK/ TPA/
Eptifibatide / IIb/IIIa?	Yes / No	
Beta Blocker?	Yes / No	

Nitrate?	Yes / No
Statin?	Yes / No
ACEI?	Yes / No
Other?	
Complications?	

Initial Outcome

For Angiogram?	Yes / No
Angio result	
Treatment plan	Med / CABG / PTCA
Revascularisation details?	
Final ECG	Non Q / Q / BBB

Admission Blood Results

Haemoglobin	
Haematocrit	
White Cell Count and differential	
Platelets and MPV	
Creatinine	
Serum cholesterol	
Triglycerides	
HDL	
LDL	

glucose	
CRP (done in hospital)	
Troponin	
CK	

This interview will be divided up into several sections in which some of the questions might seem to be more relevant to your heart problem than others. Any information you provide us will be kept strictly confidential.

Are you ready to begin?

BACKGROUND INFORMATION

To start with I'd like to gather some general background information about you.

1. How old are you? .....

2. Date of Birth ____ ____ ____

3. Gender: Male Female

4. Weight ..... Height ..... BMI (later) .....

5. What is your marital status?

   Single Married Divorced Widowed
   Separated Living as Married Other.....

6. What category do you feel best describes your ethnic origin?

   African Asian Middle Eastern
   Oriental White European White non-European Caribbean
   Other.....

7. What educational qualifications do you have?

   None ....
   School Certificate .... CSE's... ....
   GCSE's, O levels.. .... A levels.. ....
   Degree .... Other.....

8. How old were you when you left formal education? .....

9. With whom do you live (note how many people in total)?

Parents.....		Spouse.....		Friends	.....
Children	.....	Other relatives.....		Rest/care home	.....

10. Can you count on anyone to give you emotional support (e.g. talking over problems to help you with a difficult decision)?

Yes No No need of help

(If Yes) How many people would give you this kind of support? .....

11. When you need some extra help, can you count on anyone to help with daily tasks like grocery shopping, house cleaning, cooking, telephoning, giving you a lift somewhere?

Yes No No need of help

(If Yes) How many people would give you this kind of support? .....

12. Do you rent or own your own home? .....

13. How many rooms are in your home (excluding bathroom and kitchen)? .....

14. Do you have use of a car/van? Yes / No

15. Were you employed at the time of your heart problem? If so, what was the nature of your employment?

Full time	....	Part time	....	Volunteer	....		
Disabled	....	Unemployed	....	Self employed	....	Retired....	

Job title .....

If retired, what was your last major occupation? .....

(If married female) What is/was your husband's occupation? .....

16. What is your current source of income? .....

17. What is your approximate personal yearly income, before tax is deducted? (If retired, any incoming money, as well as pension).

Under £10,000	....
£10,000 - £20,000	....
£20,000 - £30,000	....
£30,000 - £40,000	....
Over £40,000	....

18. What total income has your household received in the last 12 months? Please include your own income and that of others from any source, including wages, interest from savings, investment dividends, rent or property, and benefits.

Under £10,000	....
£10,000 - £20,000	....
£20,000 - £30,000	....
£30,000 - £40,000	....
Over £40,000	....

YOUR HEALTH

19. Do you have:

Diabetes	Yes/No
(If Yes) Do you take insulin?	Yes/No
High blood pressure?	Yes/No
High cholesterol in your blood?	Yes/No

20. Do you have any other health problems **at the moment** (relevant to heart problem and/or hormonal, immune, respiratory, eating disorders, etc) and medication?

.....

.....

.....

21. Have you had any other health problems in the **past 5 years**?

.....

.....

.....

22. When did you last have a cold or 'flu? .....

23. Were you taking any medicines or pills before you were admitted to hospital?

Yes/No
If Yes, what type and for how long:

.....

.....

.....

24. Has anyone in your family had heart disease? Yes/No

If Yes, what kind of heart disease .....

Did it cause the death of your relative(s)? Yes/No

If Yes, at what age did they die? .....

25. Do you currently have or have you had in the past any kind of mental health problem (e.g. depression, anxiety (panic attacks, severe phobia) or psychosis)? Yes/No

If Yes, what did the doctor call this? .....

If Yes, what, when and any medication?.....

.....

26. Do you smoke cigarettes, cigars or pipes (specify)? Yes / No

If "Yes", please specify how many **per day in the past 6 months**, and for how long you have smoked

.....

If not a current smoker, did you smoke in the past? Yes / No

If "Yes", when did you quit smoking? .....

Are you currently taking nicotine replacement therapy? Yes / No

27. Do you drink alcohol? Yes / No

If Yes, how many units **per week over the past 6 months** on average?
(1 Unit = ½ pint of beer, 1 glass of wine or 1 measure of spirit) .....units per week

28. In the **past 6 months** have you taken any of the following drugs? If Yes, indicate average frequency.

Marijuana	Yes/No	If yes, no. times in past 6 months:.....
Cocaine	Yes/No	If yes, no. times in past 6 months:.....
Heroin	Yes/No	If yes, no. times in past 6 months:.....
Amphetamine	Yes/No	If yes, no. times in past 6 months:.....
Other (details .....)	Yes/No	If yes, no. times in past 6 months:.....

29. How many times **per week over the past 6 months** have you done vigorous physical activity enough to make you out of breath?

None 1 2 3 4 5 6+

Please specify the activity .....

30. Are you sexually active? Yes / No
If Yes, how many times **per week over the past 6 months** have you been sexually active? .....

EVENTS SURROUNDING YOUR HEART PROBLEM

31. What **time** of the day or night, and on what **date** did your heart problem occur?

.....

Able to establish time of event? Yes / No

(If not possible to establish time, abbreviate interview: go to Q's 37-39, 44-46)

32. Tell me about any heart pain you experienced in the four days before you were admitted to hospital (type and duration) .....

.....

33. If it occurred at night were you asleep or just awakening? .....

34. On the day your heart problem occurred, what time did you wake up? .....
35. What time do you normally wake up?
Time..... No habitual time?.....

What time do you normally go to sleep?
Time..... No habitual time?.....

36. Where were you when your heart problem occurred?

At home ..... Outside ..... Recreational activity .....
At work ..... In a car.....

Get details .....

.....

37. What did you think was happening when your symptoms came on (ie did you think it was your heart or something else)?.....

.....

38. How long was it between the onset of your symptoms and deciding to seek

medical help? .....

What were your reasons for this delay in seeking help?

.....

39. How long did you have to wait between deciding to seek help and

receiving medical attention? .....

What were the reasons for this delay in receiving medical attention?

.....

40. Please describe what happened during the 24 hours before your heart problem

I am now going to ask you about various behaviours and emotions that you may have experienced during certain time periods leading up to your heart problem.

41. **During 2 hours pre-event:**

(note if, e.g. 0900h–1100h, 0900h–1000h=1st hour pre-event, 1000h-1100h=2nd hour pre-event)

Think about the 2 hours before your heart problem. It was (day) and the time was .....

a. Did you do any exercise or physical activity enough to make you out of breath during this time? Yes/No

If Yes, for how long did you do this activity?

1st hr pre-event:.....mins

2nd hr pre-event:.....mins

b. Did you engage in sexual activity during this time?

1st hr pre-event: Yes / No

2nd hr pre-event: Yes / No

c. Did you take any recreational drugs during this time?

1st hr pre-event: Yes / No

2nd hr pre-event: Yes / No

(If Yes) What did you take? .....

d. Did you smoke during this time? Yes/No

(If Yes) no. smoked and what smoked 1st hr pre-event:.....

no. smoked and what smoked 2nd hr pre-event:.....

d. Did anything unusual occur during this time, for example, had you eaten a very large or fatty meal; had you had a large quantity of alcohol?

1st hr pre-event: Yes/No

2nd hr pre-event: Yes/No

If Yes, description of unusual occurrence.....

If Yes, no. times unusual occurrence over past 6 months .....

f. Were you irritated or angry during this time? Yes/No

If Yes, show card. These are varying levels of irritation and anger. For each of these hours, how you would describe how irritated or angry you were....

(record highest **level** of anger reached, an estimate of **how long** the anger lasted, and the **reason** for the anger)

1st hour - .....

.....

2nd hour - .....

.....

g. Were you tense or stressed during this time? Yes/No

If Yes, show card. These are varying levels of tension and stress. For each of these hours, how you would describe how tense or stressed you were....

(record highest **level** of stress reached, an estimate of **how long** the stress lasted, and the **reason** for the stress)

1st hour - .....

.....

2nd hour - .....

.....

h. Were you sad or depressed during this time? Yes/No

If Yes, show card. These are varying levels of sadness and depression. For each of these hours, how you would describe how sad or depressed you were....

(record highest **level** of depression reached, an estimate of **how long** the depression lasted, and the **reason** for the depression)

1st hour - .....

.....

2nd hour - .....

.....

42. **During same 2 hours previous day:**

Now think about the same 2 hours the day before your heart problem; that was (day) between the times of ..... and .....

a. Did you do any exercise or physical activity enough to make you out of breath during this time? Yes/No

If Yes, for how long did you do this activity?

1st hr prev.day:.....mins

2nd hr prev.day:.....mins

b. Did you engage in sexual activity during this time? 1st hr prev.day: Yes / No

2nd hr prev.day: Yes / No

c. Did you take any recreational drugs during this time? 1st hr prev.day: Yes / No

2nd hr prev.day: Yes / No

(If Yes) What did you take? .....

d. Did you smoke during this time? Yes/No

(If Yes) no. smoked and what smoked 1st hr prev.day:.....

no. smoked and what smoked 2nd hr prev.day:.....

e. Did anything unusual occur during this time, for example, had you eaten a very large or fatty meal; had you had a large quantity of alcohol? 1st hr prev.day: Yes/No

2nd hr prev.day: Yes/No

If Yes, description of unusual occurrence.....

If Yes, no. times unusual occurrence over past 6 months .....

f. Were you irritated or angry during this time? Yes/No

If Yes, show card. These are varying levels of irritation and anger. For each of these hours, how you would describe how irritated or angry you were....

(record highest **level** of anger reached, an estimate of **how long** the anger lasted, and the **reason** for the anger)

1st hour - .....

.....

2nd hour - .....

.....

g. Were you tense or stressed during this time? Yes/No

If Yes, show card. These are varying levels of tension and stress. For each of these hours, how you would describe how tense or stressed you were....

(record highest **level** of stress reached, an estimate of **how long** the stress lasted, and the **reason** for the stress)

1st hour - .....

.....

2nd hour - .....

.....

h. Were you sad or depressed during this time? Yes/No

If Yes, show card. These are varying levels of sadness and depression. For each of these hours, how you would describe how sad or depressed you were....

(record highest **level** of depression reached, an estimate of **how long** the depression lasted, and the **reason** for the depression)

1st hour - .....

.....

2nd hour - .....

.....

43. **During 24 hours prior to event:**

I'd now like you to think of the whole 24 hours before your heart problem occurred, from (time) on (day) until two hours before the time your symptoms began.

a. Did you do any exercise or physical activity enough to make you out of breath during this time? Yes/No

If Yes, for how long did you do this activity? .....

b. Did you engage in sexual activity during this time? Yes/No

c. Did you take any recreational drugs during this time? Yes/No

(If Yes) What did you take? .....

d. Did you smoke during this time? Yes/No

(If Yes) Details .....

e. Did anything unusual occur during this time, for example, had you eaten a very large or fatty meal; had you had a large quantity of alcohol?

.....

If Yes, ask for estimated usual frequency ...../dy, wk, mth

f. Were you irritated or angry during this time? Yes/No

If Yes, show card. How you would describe how irritated or angry you were....

(record highest **level** of anger reached, an estimate of **how long** the anger lasted, and the **reason** for the anger)

.....

.....

.....

g. Were you tense or stressed during this time? Yes/No

If Yes, show card. These are varying levels of tension and stress. For each of these hours, how you would describe how tense or stressed you were....

(record highest **level** of stress reached, an estimate of **how long** the stress lasted, and the **reason** for the stress)

.....

.....

.....

h. Were you sad or depressed during this time? Yes/No

If Yes, show card. These are varying levels of sadness and depression. For each of these hours, how you would describe how sad or depressed you were....

(record highest **level** of depression reached, an estimate of **how long** the depression lasted, and the **reason** for the depression)

.....

.....

.....

44. **During previous 6 months:**

I'd now like you to think of the 6 months leading up to your heart problem; from (month) to (this month).

a. Were you ever irritated or angry during this time? Yes/No

If Yes, show card. These are varying levels of irritation and anger. Could you tell me how often (estimated usual frequency) during the 6 months you were....

(for each: could you give me an idea of the length of time you felt this way each time)

1 - no. of occurrences ..... length of time per occurrence .....

2 - no. of occurrences ..... length of time per occurrence .....

3 - no. of occurrences ..... length of time per occurrence .....

4 – no. of occurrences ..... length of time per occurrence .....

Any particular reasons? .....

b. Were you ever tense or stressed during this time? Yes/No

If Yes, show card. These are varying levels of tension and stress. Could you tell me how often (estimated usual frequency) during the 6 months you were....

(for each: could you give me an idea of the length of time you felt this way each time)

1 - no. of occurrences ..... length of time per occurrence .....

2 - no. of occurrences ..... length of time per occurrence .....

3 - no. of occurrences ..... length of time per occurrence .....

4 – no. of occurrences ..... length of time per occurrence .....

Any particular reasons? .....

c. Were you ever sad or depressed during this time? Yes/No

If Yes, show card. These are varying levels of sadness and depression. Could you tell me how often (estimated usual frequency) during the 6 months you were....

(for each: could you give me an idea of the length of time you felt this way each time)

1 - no. of occurrences ..... length of time per occurrence .....

2 - no. of occurrences ..... length of time per occurrence .....

3 - no. of occurrences ..... length of time per occurrence .....

4 – no. of occurrences ..... length of time per occurrence .....

Any particular reasons? .....

This is the final section of the structured interview. I'm now going to ask you about anything upsetting or stressful that may have happened in the time leading up to your heart problem.

45. **During previous month:**

a. Think about the past 4 weeks. Did anything particularly bad, upsetting or stressful happen during this time?

I'll now ask you about some specific situations.

b. In the past 4 weeks has your relationship with your partner been stressful? Yes/No/NA
(If Yes, show card) How stressful has it been? 1 2 3 4

c. In the past 4 weeks has your relationship with your family been stressful? Yes/No/NA
(If Yes, show card) How stressful has it been? 1 2 3 4

d. In the past 4 weeks has work been stressful? Yes/No/NA
(If Yes, show card) How stressful has it been? 1 2 3 4

e. Other than your heart problem, have you experienced any illnesses in the past 4 weeks that you have found stressful?

Yes/No

(If Yes, show card) How stressful was that? 1 2 3 4

f. In the past 4 weeks have you felt more tired/fatigued than usual? Yes/No

46. **During previous 6 months:**

a. Now I'm going to ask you to think about the past 6 months, from (month) to (current month). Did anything particularly bad, upsetting or stressful happen during this time?

I'll now ask you about some specific situations.

b. In the past 6 months has your relationship with your partner been stressful? Yes/No/NA

(If Yes, show card) How stressful has it been? 1 2 3 4

c. In the past 6 months has your relationship with your family been stressful? Yes/No/NA

(If Yes, show card) How stressful has it been? 1 2 3 4

d. In the past 6 months has work been stressful? Yes/No/NA

(If Yes, show card) How stressful has it been? 1 2 3 4

e. Other than your heart problem, have you experienced any illnesses in the past 6 months that you have found stressful? Yes/No

(If Yes, show card) How stressful was that? 1 2 3 4

f. In the past 6 months have you felt more tired/fatigued than usual? Yes/No

That's the end of the structured interview. (If pt not too tired) Could you tell me whether you have a theory of your own about what triggered your heart problem? i.e. what brought it on?

Interviewer Impression

Any trigger? Yes No Maybe If Yes, what? .....

Did the patient frequently contradict him/herself or give information that s/he would have no way of knowing? Yes No

Did the patient appear reluctant to answer questions and thus might not have given complete information? Yes No

Are there any missing data? Yes No If Yes, why?

.....

Any other comments of interest/importance (e.g. interesting stories, unclear issues)?

Notes

When recording narrative, in the case of any unusual types of events (e.g. Skydive, Public Speech), ask usual frequency.

Q's 40 (f,g,h), 41 (f,g,h), 42 (f,g,h):

Whatever highest level reported, make an additional note of length of time lower levels lasted. For example, if patient reports highest level as level 4, make an additional note of how long levels 3, 2 and 1 occurred.

Appendix iv Anger, stress and depression rating scales

Level of anger	Description
1- mild	Enough that people notice that you're irritated
2 – moderately	Body tense, clenching fists or teeth
3 – very	Furious, almost out of control, slamming doors, banging tables
4 – extremely	Enraged. Out of control, throwing objects, hurting yourself or others

Level of Depression	Description
1- mild	"down", gloomy, not enjoying things much
2 – moderately	Feeling sad and disappointed, feeling like crying, unable to concentrate
3 – very	Feeling very sad, crying, not enjoying anything, unable to face daily life
4 – extremely	Feeling unbearably unhappy, hopeless and useless

Level of stress	Description
1- mild	Feeling rushed, too many problems, uneasy
2 – moderately	Feeling preoccupied with problems, restless, unable to relax, short with other people
3 – very	Overloaded with problems, very difficult to cope
4 – extremely	Under overwhelming pressure, unable to cope, life out of control

Appendix 5 ACCENT study questionnaire pack

Name: ..... Date: ..... Pt No: .....

Medical Research Study

Emotions and Heart Disease

Thank you very much for participating in this study of emotions and heart disease. In addition to the interview we have given you, we would like you to complete this questionnaire about your lifestyle, your attitudes and opinions, the way you feel about yourself and the way you feel about your heart problem. You may feel that some of the questions do not apply to you, but please answer each question with the answer that most closely fits the way you feel.

The answers you provide in this questionnaire will be kept **strictly confidential**. The information will go into the statistics for the study, and it will not be possible to identify you personally in any reports. Under no circumstances will any of the information you give us be made available to anyone else.

Most of the questions can be answered by circling the appropriate answer.

For example:

"It's easy for me to relax."

Strongly disagree	Disagree	Neutral	Agree	Strongly agree

Please be sure to read the instructions to each section carefully.

Thank you very much for your participation. If you have any difficulty with any questions, we can discuss it when we come to collect the questionnaire.

What do you think caused your heart problem?

Serious heart disease may be caused by many different factors. We would like to find out what factors you think were involved with your own illness. Listed below are a series of factors that patients in the past have thought helped to cause their heart disease symptoms. Please think about each item, then circle the answer that indicates how much you agree or disagree with each statement.

Factors that might have helped cause my illness:			
My illness is hereditary – it runs in my family	**No**	**Maybe**	**Yes**
Smoking played a major role in causing my illness	**No**	**Maybe**	**Yes**
My illness was brought on by other medical problems	**No**	**Maybe**	**Yes**
Stress was a major factor in my illness	**No**	**Maybe**	**Yes**
Being overweight caused my illness	**No**	**Maybe**	**Yes**
High blood pressure was an important factor in my illness	**No**	**Maybe**	**Yes**
Diet played a major role in causing my illness	**No**	**Maybe**	**Yes**
I became ill because I over-exerted myself	**No**	**Maybe**	**Yes**
It was just by chance and bad luck that I became ill	**No**	**Maybe**	**Yes**
My illness was caused by poor medical care in the past	**No**	**Maybe**	**Yes**
Lack of exercise was a cause of my illness	**No**	**Maybe**	**Yes**
My illness was brought on by tiredness and exhaustion	**No**	**Maybe**	**Yes**
Genetic factors (genes) caused my illness	**No**	**Maybe**	**Yes**

My state of mind played a major part in causing my illness	**No**	**Maybe**	**Yes**
Working too hard caused my illness	**No**	**Maybe**	**Yes**
A germ or virus caused my illness	**No**	**Maybe**	**Yes**

These questions concern the way you feel about your heart problem. Please indicate the extent you agree with each of the following statements. Circle one answer for each statement. Please try to be as accurate and honest as you can and try not to let your answers to one question influence your answers to another question. There are no right or wrong answers.

1. I was not at all afraid when my symptoms first occurred.

Strongly disagree	*Disagree*	*Agree*	*Strongly agree*

2. I am a carefree, jovial person.

Strongly disagree	*Disagree*	*Agree*	*Strongly agree*

3. I was not at all afraid when I learned that I had had a heart problem.

Strongly disagree	*Disagree*	*Agree*	*Strongly agree*

4. I do not fear dying at all.

Strongly disagree	*Disagree*	*Agree*	*Strongly agree*

5. I very seldom take unnecessary risks.

Strongly disagree	*Disagree*	*Agree*	*Strongly agree*

6. My friends worry much more about my well-being than I do.

Strongly disagree	*Disagree*	*Agree*	*Strongly agree*

7. I seldom change the way I describe my heart problem to others, no matter who they are.

Strongly disagree	*Disagree*	*Agree*	*Strongly agree*

8. I am very calm even when faced with serious difficulties.

Strongly disagree	*Disagree*	*Agree*	*Strongly agree*

Your reactions to your heart problem

We are interested to find out more about your experiences when your heart symptoms came on. Listed below are a series of things that other patients say they have felt in this situation. Please indicate the extent to which each statement is true for you. Circle one answer for each statement. Some of the later questions ask you about the "event" – what is meant by this is the heart attack or sudden worsening of angina symptoms that led to you coming into hospital.

1. I had moments of losing track of what was going on – I "blanked out", or in some way felt that I was not part of what was going on.

Not at all true	Slightly true	Somewhat true	Very true	Extremely true

2. I found that I was on "automatic pilot" – I ended up doing things that I later realised I hadn't actively decided to do.

Not at all true	Slightly true	Somewhat true	Very true	Extremely true

3. My sense of time changed – things seemed to be happening in slow motion.

Not at all true	Slightly true	Somewhat true	Very true	Extremely true

4. What was happening seemed unreal to me, like I was in a dream or watching a film or play.

Not at all true	Slightly true	Somewhat true	Very true	Extremely true

5. I felt as though I was a spectator watching what was happening to me, as if I was floating above the scene or observing it as an outsider.

Not at all true	Slightly true	Somewhat true	Very true	Extremely true

6. I was surprised to find out afterward that a lot of things had happened at the time that I was not aware of, especially things I ordinarily would have noticed.

Not at all true	Slightly true	Somewhat true	Very true	Extremely true

7. I felt confused; there were moments when I had difficulty making sense of what was happening.

Not at all true	Slightly true	Somewhat true	Very true	Extremely true

8. Memories of the event keep entering my mind.

Not at all true	Slightly true	Somewhat true	Very true	Extremely true

9. I feel very upset when I am reminded of the event.

Not at all true	Slightly true	Somewhat true	Very true	Extremely true

10. I have had bad dreams or nightmares about the event.

Not at all true	Slightly true	Somewhat true	Very true	Extremely true

11. I have "flashbacks" about the event.

Not at all true	Slightly true	Somewhat true	Very true	Extremely true

12. I was frightened when the symptoms came on.

Not at all true	Slightly true	Somewhat true	Very true	Extremely true

13. I thought that I might be dying when the symptoms came on.

Not at all true	Slightly true	Somewhat true	Very true	Extremely true

14. I found my cardiac event stressful.

Not at all true	Slightly true	Somewhat true	Very true	Extremely true

This section of the questionnaire is concerned with how many people you see or talk to **on a regular basis** including family, friends, workmates, neighbours, etc. Please circle your answer to each question.

1. What is your marital status at the moment?

Single, or never married	Married, or living with your partner	Divorced, widowed or separated

2. Do you have children?

Yes	No

If Yes, how often do you see or talk on the phone to your children?

Never	Once a month	Once every two weeks	Once a week	Every day

3. Are either of your parents living?

Yes	No

If your mother is living, how often do you see or talk on the phone to her?

Never	Once a month	Once every two weeks	Once a week	Every day

If your father is living, how often do you see or talk on the phone to him?

Never	Once a month	Once every two weeks	Once a week	Every day

4. If you are married or living with your partner, are either of your in-laws (spouse's parents) living?

Yes	No

If your mother-in-law is living, how often do you see or talk on the phone to her?

Never	Once a month	Once every two weeks	Once a week	Every day

If your father-in-law is living, how often do you see or talk on the phone to him?

Never	Once a month	Once every two weeks	Once a week	Every day

5. Are there other relatives who you feel close to?

Yes	No

If Yes, how often do you see or talk on the phone to these relatives?

Never	Once a month	Once every two weeks	Once a week	Every day

6. Do you have friends who you feel close to (i.e., people you feel at ease with, can talk to about private matters, and can call on for help)?

Yes	No

If Yes, how often do you see or talk on the phone to these friends?

Never	Once a month	Once every two weeks	Once a week	Every day

7. Do you belong to a church, temple, mosque or other religious group?

Yes	No

If Yes, how often do you talk to members of this religious group?

Never	Once a month	Once every two weeks	Once a week	Every day

8. Do you attend any classes (school, university, technical training, or adult education)
on a regular basis?

Yes	No

If Yes, how often do you talk to fellow students or teachers?

Never	Once a month	Once every two weeks	Once a week	Every day

9. If you are currently working, how often do you talk to people (other than those you supervise) at work?

Never	Once a month	Once every two weeks	Once a week	Every day

10. How often do you visit or talk to your neighbours?

Never	Once a month	Once every two weeks	Once a week	Every day

11. Are you currently involved in any regular volunteer work?

Yes	No

If Yes, how often do you talk to people involved in this work?

Never	Once a month	Once every two weeks	Once a week	Every day

12. Do you belong to any non-religious groups? Examples include social clubs, recreational groups, trades unions, etc.

Yes	No

If Yes, how often do you talk to fellow group members?

Never	Once a month	Once every two weeks	Once a week	Every day

Below are a number of statements that people often use to describe themselves. Read each statement and then circle your answer. There are no right or wrong answers; the only thing that matters is **how you generally feel.**

1. I am happy most of the time.

False	Rather false	Neutral	Rather true	True

2. I take a gloomy view of things.

False	Rather false	Neutral	Rather true	True

3. I often talk to strangers.

False	Rather false	Neutral	Rather true	True

4. I have little impact on other people.

False	Rather false	Neutral	Rather true	True

5. I find it hard to express my opinions to others.

False	Rather false	Neutral	Rather true	True

6. The future seems hopeful to me.

False	Rather false	Neutral	Rather true	True

7. I often find myself taking charge in group situations.

False	Rather false	Neutral	Rather true	True

8. I find it hard to make "small talk".

False	Rather false	Neutral	Rather true	True

9. I am often in a bad mood.

False	Rather false	Neutral	Rather true	True

10. I often feel unhappy.

False	Rather false	Neutral	Rather true	True

11. I make contact easily when I meet people.

False	Rather false	Neutral	Rather true	True

12. I often find myself worrying about something.

False	Rather false	Neutral	Rather true	True

13. I like to be in charge of things.

False	Rather false	Neutral	Rather true	True

14. When socialising, I don't find the right things to talk about.

False	Rather false	Neutral	Rather true	True

15. I feel at ease most of the time.

False	Rather false	Neutral	Rather true	True

16. I am often down in the dumps.

False	Rather false	Neutral	Rather true	True

Below are some statements that describe people's beliefs and attitudes and the way they might react to some situations. If the statement applies to you or describes you in general, circle **TRUE**. If the statement does not describe you, circle **FALSE**.

1. When someone does me a wrong I feel I should pay them back if I can, just for the principle of the thing.	TRUE	FALSE
2. I have often had to take orders from someone who did not know as much as I did.	TRUE	FALSE
3. I think a great many people exaggerate their misfortunes in order to gain the sympathy and help of others.	TRUE	FALSE
4. It takes a lot of argument to convince most people of the truth.	TRUE	FALSE
5. I think most people would lie to get ahead.	TRUE	FALSE
6. Someone has it in for me.	TRUE	FALSE
7. Most people are honest chiefly because they are afraid of being caught.	TRUE	FALSE
8. Most people will use somewhat unfair means to gain profit or an advantage rather than to lose it.	TRUE	FALSE

9. I commonly wonder what hidden reason another person may have for doing something nice for me.	TRUE	FALSE
10. It makes me impatient when people ask my advice or otherwise interrupt me when I am working on something important.	TRUE	FALSE
11. I feel that I have often been punished without cause.	TRUE	FALSE
12. Some of my family have habits that bother and annoy me very much.	TRUE	FALSE
13. My relatives are nearly all in sympathy with me.	TRUE	FALSE
14. My way of doing things is apt to be misunderstood by others.	TRUE	FALSE
15. I don't blame anyone for trying to grab everything they can get in this world.	TRUE	FALSE
16. No one cares much what happens to you.	TRUE	FALSE
17. I can be friendly with people who do things which I consider wrong.	TRUE	FALSE
18. It is safer to trust nobody.	TRUE	FALSE
19. I do not blame a person for taking advantage of people who leave themselves open to it.	TRUE	FALSE
20. I have often felt that strangers were looking at me critically.	TRUE	FALSE
21. Most people make friends because friends are likely to be useful to them.	TRUE	FALSE
22. I am sure I am being talked about.	TRUE	FALSE

23. Most people inwardly dislike putting themselves out to help other people.	TRUE	FALSE
24. I tend to be on my guard with people who are somewhat more friendly than I had expected.	TRUE	FALSE
25. People often disappoint me.	TRUE	FALSE
26. I am not easily angered.	TRUE	FALSE
27. I have often met people who were supposed to be experts who were no better than I.	TRUE	FALSE
28. I would certainly enjoy beating criminals at their own game.	TRUE	FALSE
29. I have at times had to be rough with people who were rude or annoying.	TRUE	FALSE
30. People generally demand more respect for their own rights than they are willing to allow for others.	TRUE	FALSE
31. There are certain people whom I dislike so much that I am inwardly pleased when they are catching it for something they have done.	TRUE	FALSE
32. I am often inclined to go out of my way to win a point with someone who has opposed me.	TRUE	FALSE
33. The man who had most to do with me when I was a child (such as my father, stepfather, etc.) was very strict with me.	TRUE	FALSE
34. I have often found people jealous of my good ideas, just because they had not thought of them first.	TRUE	FALSE
35. I do not try to cover up my poor opinion or pity of people so that they won't know how I feel.	TRUE	FALSE

36. I have frequently worked under people who seem to have things arranged so that they get credit for good work but are able to pass off mistakes onto those under them.	TRUE	FALSE
37. I strongly defend my own opinions as a rule.	TRUE	FALSE
38. Sometimes I am sure that other people can tell what I am thinking.	TRUE	FALSE
39. A large number of people are guilty of bad sexual conduct.	TRUE	FALSE

The following statements concern your attitudes and opinions. Please indicate the extent you agree with each of the following statements. Please circle one answer for each statement. There are no right or wrong answers.

1. In uncertain times, I usually expect the best.

Strongly disagree	Disagree	Neutral	Agree	Strongly agree

2. It's easy for me to relax.

Strongly disagree	Disagree	Neutral	Agree	Strongly agree

3. If something can go wrong for me, it will.

Strongly disagree	Disagree	Neutral	Agree	Strongly agree

4. I'm always optimistic about my future.

Strongly disagree	Disagree	Neutral	Agree	Strongly agree

5. I enjoy my friends a lot.

Strongly disagree	Disagree	Neutral	Agree	Strongly agree

6. It's important for me to keep busy.

Strongly disagree	Disagree	Neutral	Agree	Strongly agree

7. I hardly ever expect things to go my way.

Strongly disagree	Disagree	Neutral	Agree	Strongly agree

8. I don't get upset too easily.

Strongly disagree	Disagree	Neutral	Agree	Strongly agree

9. I rarely count on good things happening to me.

Strongly disagree	Disagree	Neutral	Agree	Strongly agree

10. Overall, I expect more good things to happen to me than bad.

Strongly disagree	Disagree	Neutral	Agree	Strongly agree

This part of the questionnaire is about your emotions and how you have been feeling since you were admitted to hospital. Read each item and circle the reply which comes closest to how you have been feeling **since you were admitted to hospital**.

1. I feel tense or 'wound up':

Most of the time	A lot of the time	From time to time, occasionally	Not at all

2. I get a sort of frightened feeling as if something awful is about to happen:

Very definitely and quite badly	Yes, but not too badly	A little, but it doesn't worry me	Not at all

3. Worrying thoughts go through my mind:

A great deal of the time	A lot of the time	From time to time	Only occasionally but not too often

4. I can sit at ease and feel relaxed:

Definitely	Usually	Not often	Not at all

5. I get a sort of frightened feeling like 'butterflies ' in the stomach:

Not at all	Occasionally	Quite often	Very often

6. I feel restless as if I have to be on the move:

Very much indeed	Quite a lot	Not very much	Not at all

7. I get sudden feelings of panic:

Very much indeed	Quite a lot	Not very much	Not at all

Medical research is constantly trying to track down the causes of disease. You would help this research by answering the following questions about **how you feel lately**. Please mark the answers that are true for you. If you don't know or cannot decide circle the ?. There are no "right" or "wrong" answers.

1. Do you often feel tired?	yes	?	no
2. Do you often have trouble falling asleep?	yes	?	no
3. Do you wake up repeatedly during the night?	yes	?	no
4. Do you feel weak all over?	yes	?	no
5. Do you have the feeling that you haven't been accomplishing much recently?	yes	?	no

6. Do you have the feeling that you can't cope with everyday problems as well as you used to?	yes	?	no
7. Do you believe that you have come to a "dead end"?	yes	?	no
8. Do you lately feel more listless than before?	yes	?	no
9. Do you enjoy sex as much as ever?	yes	?	no
10. Have you experienced a feeling of hopelessness recently?	yes	?	no
11. Does it take more time to grasp a difficult problem than it did a year ago?	yes	?	no
12. Do little things irritate you more lately than they used to?	yes	?	no
13. Do you feel you want to give up trying?	yes	?	no
14. Do you feel fine?	yes	?	no
15. Do you sometimes feel that your body is like a battery that is losing its power?	yes	?	no
16. Would you want to be dead at times?	yes	?	no
17. Do you have the feeling these days that you just don't have what it takes any more?	yes	?	no
18. Do you feel dejected?	yes	?	no
19. Do you feel like crying sometimes?	yes	?	no
20. Do you ever wake up with a feeling of exhaustion and fatigue?	yes	?	no
21. Do you have increasing difficulty in concentrating on a single subject for long?	yes	?	no

This part of the questionnaire consists of 21 groups of statements. After reading each group of statements carefully, circle the number (0, 1, 2, or 3) next to the one statement in each group which **best** describes the way you have been feeling **since you were admitted to hospital, including today**. If several statements within a group seem to apply equally well, circle each one. **Be sure to read all the statements in each group before making your choice.**

1. 0 I do not feel sad.
   1 I feel sad.
   2 I am sad all the time and I can't snap out of it.
   3 I am so sad or unhappy that I can't stand it.

2. 0 I am not particularly discouraged about the future.
   1 I feel discouraged about the future.
   2 I feel I have nothing to look forward to.
   3 I feel that the future is hopeless and that things cannot improve.

3. 0 I do not feel like a failure.
   1 I feel I have failed more than the average person.
   2 As I look back on my life, all I can see is a lot of failures.
   3 I feel I am a complete failure as a person.

4. 0 I get as much satisfaction out of things as I used to.
   1 I don't enjoy things the way I used to.
   2 I don't get real satisfaction out of anything anymore.
   3 I am dissatisfied or bored with everything.

5. 0 I don't feel particularly guilty.
   1 I feel guilty a good part of the time.
   2 I feel guilty most of the time.
   3 I feel guilty all of the time.

6. 0 I don't feel I am being punished.
   1 I feel I may be punished.
   2 I expect to be punished.
   3 I feel I am being punished.

7. 0 I don't feel disappointed in myself.
   1 I am disappointed in myself.
   2 I am disgusted with myself.
   3 I hate myself.

8. 0 I don't feel I am any worse than anybody else.
   1 I am critical of myself for my weaknesses or mistakes.
   2 I blame myself all the time for my faults.
   3 I blame myself for everything bad that happens.

9. 0 I don't have any thoughts of killing myself.
   1 I have thoughts of killing myself, but I would not carry them out.
   2 I would like to kill myself.
   3 I would kill myself if I had the chance.

10. 0 I don't cry any more than usual.
    1 I cry more now than I used to.
    2 I cry all the time now.
    3 I used to be able to cry, but now I can't cry even though I want to.

11. 0 I am no more irritated now than I ever am.
    1 I get annoyed or irritated more easily than I used to.
    2 I feel irritated all the time now.
    3 I don't get irritated at all by the things that used to irritate me.

12. 0 I have not lost interest in other people.
    1 I am less interested in other people than I used to be.
    2 I have lost most of my interest in other people.
    3 I have lost all of my interest in other people.

13. 0 I make decisions about as well as I ever could.
    1 I put off making decisions more than I used to.
    2 I have greater difficulty in making decisions than before.
    3 I can't make decisions at all any more.

14. 0 I don't feel I look any worse than I used to.
    1 I am worried that I am looking old or unattractive.
    2 I feel that there are permanent changes in my appearance that make me look unattractive.
    3 I believe that I look ugly.

15. 0 I can work about as well as before.
    1 It takes an extra effort to get started at doing something.
    2 I have to push myself very hard to do anything.
    3 I can't do any work at all.

16. 0 I can sleep as well as usual.
1 I don't sleep as well as I used to.
2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
3 I wake up several hours earlier than I used to and cannot get back to sleep.

17. 0 I don't get more tired than usual.
1 I get tired more easily than I used to.
2 I get tired from doing almost anything.
3 I am too tired to do anything.

18. 0 My appetite is no worse than usual.
1 My appetite is not as good as it used to be.
2 My appetite is much worse now.
3 I have no appetite at all anymore.

19. 0 I haven't lost much weight, if any, lately.
1 I have lost more than 5 pounds.
2 I have lost more than 10 pounds.
3 I have lost more than 15 pounds.

I am purposely trying to lose weight by eating less. Yes _____
No_____

20. 0 I am no more worried about my health than usual.
1 I am worried about physical problems such as aches and pains; or upset stomach; or constipation.
2 I am very worried about physical problems and it's hard to think of much else.
3 I am so worried about my physical problems that I cannot think about anything else.

21. 0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely.

Date questionnaire completed :_____

That is the end of the questionnaire. Please check that you have answered all of the questions. If you had any difficulty with any of the questions we can discuss it when we come to collect the questionnaire. Thank you very much for taking the time to make this important contribution to our study of emotions and heart disease. We will be in touch with you regarding the next stage of the study and look forward to seeing you soon.

Appendix vi Invitation letter

Royal Free and University College Medical School

UNIVERSITY COLLEGE LONDON

DEPARTMENT OF EPIDEMIOLOGY AND PUBLIC HEALTH

Gower Street Campus
1-19 Torrington Place
London WC1E 6BT

Telephone 44 (0) 020 7679 2000
Direct Line 44 (0) 020 7679
Fax 44 (0) 020 7813 0242

Dear,

The Stress and Coronary Artery Disease Study

In conjunction with the Department of Cardiology at the Middlesex / National Heart Hospitals we are currently carrying out medical research to try and establish the link between stress and coronary artery disease.

This research study is funded by the British Heart Foundation to try and explore how our emotions and behaviour influence the cardiovascular system in health and disease. The results of this study will help advance our knowledge of the links between the mind and the body. This exciting and important area of medical science will contribute to the understanding of heart disease, and aims to improve both the prevention and the treatment of this common illness. The study is being carried out in collaboration between Professor Andrew Steptoe from the Department of Epidemiology and Public Health at University College London and Dr Jean McEwan from the Department of Clinical Cardiology. The researchers who will carry out the work are Dr Lena Brydon, Dr Sue Edwards and Dr Philip Strike.

We would like to invite you to take part in this study. This would involve you spending a morning with us at University College in the West End of London. This would be arranged at a time convenient to you.

We will take measures such as height, weight, and blood pressure and then measure biological responses whilst carrying out two short but interesting tasks. This will be followed by a period of quiet rest. We will also give you some questionnaires to complete.

We enclose a detailed description of the study. If you would be interested in helping us with this study then please complete and return the enclosed form in the FREEPOST envelope. We hope that you do not mind being contacted in this way and that you will be able to help. If you have any questions or would like more information the please contact our research nurse Bev Murray on or Dr Philip Strike on or on

Appendix vii Patient Information Sheet

Royal Free and University College Medical School
UNIVERSITY COLLEGE LONDON

DEPARTMENT OF EPIDEMIOLOGY AND PUBLIC HEALTH

Gower Street Campus
1-19 Torrington Place
London WC1E 6BT

Study of Stress and Coronary Artery Disease

Information Sheet

Principal investigators: Professor Andrew Steptoe, Dr. J. McEwan,
Investigating team: Dr Lena Brydon and Dr. Philip Strike

What is this study about?

This study is funded by the British Heart Foundation, and aims to explore how behaviour and stress influence the cardiovascular, immune, and hormonal systems.

The results of this study will advance our knowledge of the links between the mind and the body. This exciting and important area of medical science will contribute to the understanding of heart disease, and aims to improve both the prevention and treatment of this common illness.

Who can take part?

We are focussing on a particular sub-group of the population: non-smoking (although who may have smoked in the past) men who have coronary artery disease. As one of the tasks in the study involves looking at different coloured words on a computer screen, we need volunteers who are not colour-blind. Participants should be in otherwise relatively good health. Anyone with other significant physical or psychiatric diseases (except for coronary artery disease) should not volunteer for this study. Volunteers should also not recently have received any vaccinations.

What will I have to do?

The study involves you spending a morning with us at the Department of Epidemiology and Public Health, University College London, situated on Torrington Place in the West End. When you agree to take part in the study, we will arrange a convenient date for you to attend a session, which will begin at 9:00 a.m. and end at approximately 1:00 p.m. If you happen to have a cold or flu or have had to take medicine shortly before, please get in touch beforehand so that we can reschedule the appointment. The session is quite long, so be sure

to wear comfortable clothing. When you arrive at the department, one of our team members will meet you at the reception desk and take you to the rooms where the study takes place. Before starting, we will explain everything again, ask you to fill in a consent form, and make sure that any questions you may have are answered.

What about my medications?

We would like to see the effects of stress on the body without alteration from medication. **We would like you to stop taking aspirin or clopidogrel ten days before the study** (unless you have had an angioplasty within the last month).

Please stop taking **Beta blockers** (e.g. atenolol, metoprolol),
Statins (eg simvastatin, atorvastatin), and
ACE inhibitors (e.g ramipril) **for 3 days before the study.**

We will look at your medication with you and advise you appropriately.

There should be **no** ill effects from stopping these medications for a short time. The increased risk of any dangerous problems (such as heart attack, stroke or death) would be **less than** one in 800 – so very small indeed.
We would ask that you don't take any of your medicines on the morning of the study. They can all be taken later in the day. If you have any questions at all, please contact us. If you notice any symptoms then you should restart your medicines at once.

What happens during the study?

Firstly, our research nurse will take some physical measures, namely height, weight, waist and hip circumference, and body fat mass. The latter measure requires removal of shoes and socks. At this point you will be asked to provide a saliva sample. After this you will be seated in a comfortable chair and a needle will be inserted in a vein in your lower arm or the back of your hand. Two small cuffs will be attached to two of your fingers. A blood pressure cuff will be attached to your arm at certain times, so it would be helpful if you wear clothing with loose sleeves and cuffs. In the 20 minutes following this, there will be a rest period during which you may read. Please bring something along to read if you want (provided it is fairly relaxing!), or you can read one of our magazines. You will then be asked to perform two 5-minute tasks; a visual puzzle and a hand-eye co-ordination task. These tasks do not require any special skills. After the tasks you can relax again, this time for two hours, during which time you can read; we will also ask you to complete some questionnaires during this time. After the session we provide you with refreshments and will be happy to discuss all that happened during the session and answer any additional questions you may have.

What measurements do we want to take from you and how will it be done?

Measurements of blood pressure - During the session, two small cuffs placed around the fingers of one hand will measure your blood pressure. You will feel the cuffs pulsating

slightly, but you'll soon get used to this sensation and it will not be uncomfortable. We will also take blood pressure measurements now and again with a cuff placed around the arm.

Saliva measurements - You will be asked to provide seven saliva samples throughout the session, by placing a small cotton swab under the tongue for 2 minutes. The saliva samples will allow assessment of hormone activity.

Blood measurements - In order to examine immune function, we will need to take some blood from you during the session. This is why we insert a needle in the back of your hand or lower arm. This needle remains comfortably in place throughout the session. The insertion of the needle may cause slight discomfort at first, which is why we give you a 20-minute rest afterwards to get used to the needle. We draw blood samples from the inserted needle five times throughout the session. This is a painless procedure, and is designed to cause minimum discomfort. The measurements we obtain from your blood are indicators of immune activity. We will also look at the make-up of certain cytokine genes. Other blood measurements we look at include clotting factors, glucose and cholesterol.

What are the benefits?

We will give you information about your blood pressure and heart rate after the session and, if you wish, will give you feedback on your cholesterol levels after they have been analysed. Importantly, you will be helping us understand more about the way different behaviours and medications affect the body, and this research may help you and other people in the long term.

If I take part, what about my travel costs?

We will pay your travel expenses. Please keep receipts for any travel costs.

What if I change my mind during the study?

If at any point and for any reason you do not want to carry on, then you may stop. There are no consequences of withdrawal from the study.

What happens to the information?

All the information that we get from this study about you, including your name, will be confidential, and will only be used for medical research purposes. Data from all volunteers will be combined and it will not be possible to identify individuals within published results. We will be doing analyses on certain genes that we believe may be important. This will not affect your eligibility for life insurance.

At the end of the study, we shall send you a brief summary of our findings.

Do I have to sign anything?

We will ask you to sign a Consent Form. This is to show that you understand what is involved and that you have read this Information Sheet. You can still withdraw from the study at any time.

What if I have more questions or do not understand something?

If you have any queries, or would like more information about the study, please feel free to telephone the research team at 020 7679 1688 or e-mail philip@public-health.ucl.ac.uk. Any member of our team will be happy to answer your questions. Since we cannot always be in our office, you might get an answer machine, but if you leave your name and telephone number, a member of our team will get back to you as soon as possible.

Appendix viii Session instructions

INSTRUCTIONS FOR PARTICIPANTS

- Please read the information sheet prior to the session.
- The evening before the session, please try to drink plenty of water.
- Please do **not** take part in strenuous exercise or drink alcohol from the evening before the session.
- We would like you to have breakfast (e.g. toast, cereal, fruit) the morning of the session, but please do not have a high-fat (i.e. fried foods) or high-protein (i.e. meat) breakfast.
- Please do not drink coffee, tea, coca-cola or other drinks containing caffeine on the morning of your visit. Please drink water or fruit juice instead.
- Please try and wear (or bring) comfortable clothing with loose sleeves/cuffs.
- Remember to keep all receipts for reimbursement of your travel expenses.
- If possible, we would be grateful if you could provide us with your birth weight when you attend the session.
- Please remember that we need to reschedule your appointment if you have a cold on the day of the session or have taken aspirin or any other medication during the 10 days before the session.

Many thanks for your participation

Appendix ix Consent form

Royal Free and University College Medical School

UNIVERSITY COLLEGE LONDON

DEPARTMENT OF EPIDEMIOLOGY AND PUBLIC HEALTH

Gower Street Campus
1-19 Torrington Place
London WC1E 6BT

Telephone 44 (0) 020 7679 2000

Study Number:
Patient Identification Number for this trial:

CONSENT FORM (Confidential)

Title of project: **A Study of Stress and Coronary Artery Disease**

Name of Researcher: Professor Andrew Steptoe, Dr. Lena Brydon, Dr. Sue Edwards, Dr. Philip Strike
Any questions to Dr. Philip Strike, Department of Epidemiology and Public Health, University College London, 1-19 Torrington Place, London, WC1E 6BT. Telephone 020 7679 1804

Please initial box

1. I confirm that I have read and understood the information sheet for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that sections of any of my medical notes may be looked at by responsible individuals from (company name) or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐
4. I agree to take part in the above study. ☐

Name of patient	Date	Signature

Name of Person taking consent (if different from researcher)	Date	Signature
Researcher	Date	Signature

Appendix x Laboratory protocol

SCD STUDY PROTOCOL

Participant ID			
Date		Date of Birth	
Start time		Time of Awakening	

Cycling Lab (0900h):

- Information sheet and consent form
- Confirm health status detailed in information sheet
- Check instructions were followed: medication / alcohol / exercise / caffeine
- Time and content of last meal

  .....
- How did they travel to the session? (did anything unusual happen?)

  .....
- Brief verbal explanation of study
- First **SALIVA (1)** sample (2 min under tongue, without chewing) STOP WATCH 2 MIN

Physical Measures			
Height	m	Weight	kg
Hip measure	cm	Waist measure	cm

- TOILET

Stress Lab (0925h): *(check room temperature is 22° and prepare heat pad)*

- **(Initialise Portapres: enter physical data and set cuffs to 1-min switching interval)**
- Needle insertion and heat pad
- Attach Portapres cuffs (middle and ring) and height line (explain camera and uncrossed legs)
- Switch Portapres (PP) on (START/STOP button) to ensure both cuffs work OK

- Casual BP SBP _____ DBP _____ HR _____ (habituation)
- PP off (START/STOP button), **change to 30-min cuff interval** and leave in ready mode

Rest Period (0945h) **START CLOCK**

- **At 10 min:** PP on (START/STOP) (remember to monitor times of cuff switch)

ENSURE PP START/STOP BUTTON NOT PRESSED DURING THE SESSION

ENSURE DISPLAY READS BETWEEN 30/06 AND 30/28 BEFORE RECORDING EVENTS

- **At 25 min:**

  © **Calibration off** © press PP **event** button

- **At 30 min:**

  © Press PP **event** button © **calibration on** *(at 40 min, 1025h cuff switch)*

  © Rest Questionnaire

  © Casual BP SBP _____ DBP _____ HR _____

  wait 1 minute, sitting quietly

  © Casual BP SBP _____ DBP _____ HR _____

  © **SALIVA (2)** STOP WATCH 2 MIN and **BLOOD (1)** Start time ..... Stop time .....

Stress Tasks (1030h) *(Change heat pad and set up Stroop)*

STROOP

- Give written instructions (while line is being flushed)
- Talk participant through the practice
- Let the participant have a go at the practice until they have the idea (within reason)
- **Calibration off** © start Stroop (F3 return)© press PP **event** button
- At end of task, press PP **event** button © **calibration on**
- Task impact questionnaire

MIRROR

- Give written instructions
- Let the participant practice until they have the idea (within reason). Re-set errors.

- **Calibration off** © "start tracing now" © start stopwatch © press PP **event** button
- After 5 min, "stop tracing" © press PP **event** button © **calibration on**
- Record no. of tracings _____ and no. of errors _____
- Task impact questionnaire

Recovery period (1050 – 1400h) START CLOCK | TIME NOW:

(cuff switch at 1055h)

Immediately post-task:

- Casual BP SBP _____ DBP _____ HR _____
- **SALIVA (3)** STOP WATCH 2 MIN and **BLOOD (2)** Start time ..... Stop time .....

change heat pad

- Check calibration is on
- **At 15 min: SALIVA (4)** sample
- **At 25 min:**

  ©**Calibration off** © press PP **event** button
- **At 30 min:**

  © Press PP **event** button *(at 35 min: 1125h cuff switch)*

  © **Calibration on**

  © Recovery Questionnaire (1)

  © **SALIVA (5)** STOP WATCH 2 MIN and **BLOOD (3)** Start time ..... Stop time .....

(should finish by 36 min)

(Change heat pad)

** 30 min for 1st questionnaire **

(at 1h5m: 1155h cuff switch)

- **At 1h10 min:**

  ©**Calibration off** © press PP **event** button
- **At 1h15 min:**

  © Press PP **event** button

  © **Calibration on**

© Recovery Questionnaire (2)

© **SALIVA (6)** STOP WATCH 2 MIN and **BLOOD (4)** Start time ..... Stop time .....

(should finish by 1h21)

(at 1h 35min: 1225h cuff switch) *(Change heat pad)*

** 30 min for 2nd questionnaire **

- **At 1h 55m:**

  ©**Calibration off** © press PP **event** button

- **At 2h:** *(at 2h5m: 1255h cuff switch)*

  © Press PP **event** button

  © Turn Portapres off (START/STOP button)

  © Recovery Questionnaire (3)

  © **SALIVA (7)** STOP WATCH 2 MIN and **BLOOD (5)** Start time ..... Stop time .....

  (should finish by 2h6m)

- Needle out
- Take out PP air hose and cable, remove cuffs and height line, turn off at wall.

Cycling Lab (1300h):

- **At 2h 10m:**

  © Bodystat measurement (recover data after session)

- **At 2h 15m:** Lunch
- **At 2h 45m:**

  © **BLOOD (6** – separate venepuncture)

- **At 2h 50m:**

  © Carotid Ultrasound

COMMENTS ABOUT SESSION (Note anything that went wrong including button pressed out of place or missed):

From Chapter 10, Appendix xi Invitation letter

Royal Free and University College Medical School

UNIVERSITY COLLEGE LONDON

DEPARTMENT OF EPIDEMIOLOGY AND PUBLIC HEALTH

Gower Street Campus
1-19 Torrington Place
London WC1E 6BT

18/05/2004

Dear Mr ,

Many thanks for your previous help with our study on "Stress and the Heart". We are extremely grateful for all the assistance you have given us with this project. It is now over a year since your initial admission and as we have mentioned previously we would like to invite you to come along and see us at University College Hospital for a morning to see how your body handles mild to moderate stress.

Please find a copy of the Patient Information Sheet which gives you all of the information about this study.

We will give you a ring as we have done previously to see how you are and to see if you would be interested in helping us with this work. If there is a special time which it is best to contact you please let us know on the enclosed form (a freepost envelope is included). We will then be able to explain this study further and to answer any questions that you may have.

The session takes one morning and we would be able to fit it around your schedule. All your travel costs will be reimbursed. I hope that you will be able to help us.

I look forward to speaking to you soon.

Yours sincerely

Dr Philip Strike
British Heart Foundation Clinical Research Fellow

xii Patient Information Sheet UCH / Southend

Royal Free and University College Medical School

UNIVERSITY COLLEGE LONDON

DEPARTMENT OF EPIDEMIOLOGY AND PUBLIC HEALTH

Gower Street Campus
1-19 Torrington Place
London WC1E 6BT

Study of Stress and Coronary Artery Disease
Information Sheet

Investigating team: Professor Andrew Steptoe, Dr. J. McEwan, Dr P Kelly and Dr. Philip Strike

What is this study about?

This study is funded by the British Heart Foundation, and aims to explore how behaviour and stress influence the cardiovascular, immune, and hormonal systems.

We have already interviewed you regarding the circumstances surrounding your heart problem. This study is to find out more about the way that your body handles stress.
The results of this study will advance our knowledge of the links between mind and body and help the understanding of heart disease.

Who can take part?

As one of the tasks in the study involves looking at different coloured words on a computer screen, we need volunteers who are not colour-blind. Participants should be in otherwise relatively good health. Anyone with other significant physical or psychiatric diseases (except for coronary artery disease) should not volunteer for this study. Volunteers should also not recently have received any vaccinations.

What will I have to do?

The study involves you spending a morning with us at the Department of Epidemiology and Public Health, University College London, situated on Torrington Place in the West End. When you agree to take part in the study, we will arrange a convenient date for you to attend a session, which will begin at 9:00 a.m. and end at approximately 1:00 p.m. If you happen to have a cold or flu or have had to take medicine shortly before, please get in touch beforehand so that we can reschedule the appointment. The session is quite long, so be sure to wear comfortable clothing. When you arrive at the department, one of our team members will meet you at the reception desk and take you to the rooms where the study takes place. Before starting, we will explain everything again, ask you to fill in a consent form, and make sure that any questions you may have are answered.

Do I have to take part in the study?

Participation is entirely voluntary.

What about my medications?

We would like to see the effects of stress on the body without alteration from medication.
We would like you to stop taking aspirin or clopidogrel ten days before the study (unless you have had an angioplasty or stent treatment within the last month).
Please stop taking **Beta blockers** (e.g. atenolol, metoprolol),
Statins (eg simvastatin, atorvastatin), and
ACE inhibitors (e.g ramipril) **for 3 days before the study.**

We will discuss your medication with you on the telephone before the study and advise you appropriately as well as answering any questions that you may have.
There should be **no** ill effects from stopping these medications for a short time. The increased risk of any major problems (heart attack, death or stroke) would be **less than** one eighth of one percent– so very small indeed. We would ask that you don't take any of your medicines on the morning of the study. They can all be taken later in the day. If you have any questions about this please contact us. Should you notice any symptoms then you should restart your medicines at once and seek medical advice immediately.

What happens during the study?

Firstly, our research nurse will take some physical measures, namely height, weight, waist and hip circumference, and body fat mass. At this point you will be asked to provide a saliva sample. After this you will be seated in a comfortable chair and a needle will be inserted in a vein in your lower arm or the back of your hand. In the 20 minutes following this, there will be a rest period during which you may read. Please bring something along to read if you want (provided it is fairly relaxing!), or you can read one of our magazines. You will then be asked to perform two 5-minute tasks; a visual puzzle and a speaking task. These tasks do not require any special skills. After the tasks you can relax again, this time for two hours, during which time you can read; we will also ask you to complete some questionnaires during this time. After the session we provide you with refreshments and will be happy to discuss all that happened during the session and answer any additional questions you may have.

What measurements do we want to take from you and how will it be done?

Measurements of blood pressure - During the session, two small cuffs placed around the fingers of one hand will measure your blood pressure. You will feel the cuffs pulsating slightly, but you'll soon get used to this sensation and it will not be uncomfortable. We will also take blood pressure measurements now and again with a cuff placed around the arm so it would be helpful if you wear clothing with loose sleeves and cuffs.

Saliva measurements - You will be asked to provide seven saliva samples throughout the session, by placing a small cotton swab under the tongue for 2 minutes. The saliva samples will allow assessment of hormone activity.

Blood measurements - To examine immune function, we need to take some blood from you during the session. This is why we insert a needle in the back of your hand or lower arm. This needle remains comfortably in place throughout the session. The insertion of the needle may cause slight discomfort at first. We draw blood samples from the inserted needle five times throughout the session. This should be a painless procedure. The measurements we obtain from your blood are indicators of immune activity. We will also look at certain genes involved with the immune system.

What are the benefits?

We will tell you about your blood pressure and heart rate after the session and give you feedback on your cholesterol levels after they have been analysed. Importantly, you will be helping us understand more about the way different behaviours and medications affect the body, and this research may help you and other people in the long term.

If I take part, what about my travel costs?

We will pay your travel expenses. Please keep receipts for any travel costs.

What if I change my mind during the study?

If at any point and for any reason you do not want to carry on, then you may stop. There are no consequences of withdrawal from the study.

What happens to the information?

All the information that we get from this study about you, including your name, will be confidential, and only used for medical research purposes at UCL. Data is securely stored under the care of Professor Steptoe. Data from all volunteers will be combined anonymously and it will not be possible to identify individuals within published results. We will be doing analyses on certain genes that we believe may be important. This will not affect your eligibility for life insurance. Data will be retained for 5 years. At the end of the study, we shall send you a brief summary of our findings.

Do I have to sign anything?

We will ask you to sign a Consent Form. This shows that you understand what's involved and have read this Information Sheet. You can still withdraw from the study at any time.

What if I have more questions or do not understand something?

If you have any queries, or would like more information about the study, please feel free to telephone the research team at 020 7679 1688. Any member of our team will be happy to answer your questions. Since we cannot always be in our office, you might get an answer machine, but if you leave your name and telephone number, we will get back to you as soon as possible.

St George's Healthcare NHS Trust

Appendix xiii Patient Information Sheet St George's

St George's Hospital
Blackshaw Road
London
SW17 OQT

PATIENT INFORMATION

Title of project: **Study of Stress and Coronary Artery Disease**

Names of Researchers: Professor Andrew Steptoe, Dr Jean McEwan, Dr. Philip Strike, Dr Lena Brydon, Ms Linda Perkins-Porras, Ms Daisy Whitehead

What is this study about?

This study is funded by the British Heart Foundation, and aims to explore how behaviour and stress influence the cardiovascular, immune, and hormonal systems.

We have already interviewed you regarding the circumstances surrounding your heart problem. This study is to find out more about the way that your body handles stress.
The results of this study will advance our knowledge of the links between mind and body and help the understanding of heart disease.

Who can take part?

As one of the tasks in the study involves looking at different coloured words on a computer screen, we need volunteers who are not colour-blind. Participants should be in otherwise relatively good health. Anyone with other significant physical or psychiatric diseases (except for coronary artery disease) should not volunteer for this study. Volunteers should also not recently have received any vaccinations.

What will I have to do?

The study involves you spending a morning with us at the Department of Epidemiology and Public Health, University College London, situated on Torrington Place in the West End. When you agree to take part in the study, we will arrange a convenient date for you to attend a session, which will begin at 9:00 a.m. and end at approximately 1:00 p.m. If you happen to have a cold or flu or have had to take medicine shortly before, please get in touch beforehand so that we can reschedule the appointment. The session is quite long, so be sure to wear comfortable clothing. When you arrive at the department, one of our team members will meet you at the reception desk and take you to the rooms where the study takes place. Before starting, we will explain everything again, ask you to fill in a consent form, and make sure that any questions you may have are answered.

Do I have to take part in the study?

Participation is entirely voluntary.

What about my medications?

We would like to see the effects of stress on the body without alteration from medication.
We would like you to stop taking aspirin or clopidogrel ten days before the study (unless you have had an angioplasty or stent treatment within the last month).
Please stop taking **Statins** (eg simvastatin, atorvastatin), and
ACE inhibitors (e.g ramipril) **for 3 days before the study.**

If you are taking **Beta blockers** (e.g. atenolol, metoprolol), you should carry on with these as usual.
We will discuss your medication with you on the telephone before the study and advise you appropriately as well as answering any questions that you may have. There should be **no** ill effects from stopping these medications for a short time. The increased risk of any major problems (heart attack, death or stroke) would be **less than** one eighth of one percent– so very small indeed. We would ask that you don't take any of your medicines on the morning of the study. They can all be taken later in the day. If you have any questions about this please contact us. Should you notice any symptoms then you should restart your medicines at once and seek medical advice immediately.

What happens during the study?

Firstly, our research nurse will take some physical measures, namely height, weight, waist and hip circumference, and body fat mass. At this point you will be asked to provide a saliva sample. After this you will be seated in a comfortable chair and a needle will be inserted in a vein in your lower arm or the back of your hand. In the 20 minutes following this, there will be a rest period during which you may read. Please bring something along to read if you want (provided it is fairly relaxing!), or you can read one of our magazines. You will then be asked to perform two 5-minute tasks; a visual puzzle and a speaking task. These tasks do not require any special skills. After the tasks you can relax again, this time for two hours, during which time you can read; we will also ask you to complete some questionnaires during this time. After the session we provide you with refreshments and will be happy to discuss all that happened during the session and answer any additional questions you may have.

What measurements do we want to take from you and how will it be done?

Measurements of blood pressure - During the session, two small cuffs placed around the fingers of one hand will measure your blood pressure. You will feel the cuffs pulsating slightly, but you'll soon get used to this sensation and it will not be uncomfortable. We will also take blood pressure measurements now and again with a cuff placed around the arm so it would be helpful if you wear clothing with loose sleeves and cuffs.

Saliva measurements - You will be asked to provide seven saliva samples throughout the session, by placing a small cotton swab under the tongue for 2 minutes. The saliva samples will allow assessment of hormone activity.

Blood measurements - To examine immune function, we will need to take some blood from you during the session. This is why we insert a needle in the back of your hand or lower arm. This needle remains comfortably in place throughout the session. The insertion of the needle may cause slight discomfort at first. We draw blood samples from the inserted needle five times throughout the session. This should be a painless procedure. The measurements we obtain from your blood are indicators of immune activity. We will also look at the make-up of certain genes involved with the immune system.

What are the benefits?

We will give you information about your blood pressure and heart rate after the session and, if you wish, will give you feedback on your cholesterol levels after they have been analysed. Importantly, you will be helping us understand more about the way different behaviours and medications affect the body, and this research may help you and other people in the long term.

If I take part, what about my travel costs?

We will pay your travel expenses. Please keep receipts for any travel costs.

What if I change my mind during the study?

If at any point and for any reason you do not want to carry on, then you may stop. There are no consequences of withdrawal from the study.

What happens to the information?

All the information that we get from this study about you, including your name, will be confidential, and only used for medical research purposes at UCL. Data is securely stored under the care of Professor Steptoe. Data from all volunteers will be combined anonymously and it will not be possible to identify individuals within published results. We will be doing analyses on certain genes that we believe may be important. This will not affect your eligibility for life insurance. Data will be retained for 5 years.

At the end of the study, we shall send you a brief summary of our findings.

Do I have to sign anything?
We will ask you to sign a Consent Form. This is to show that you understand what is involved and that you have read this Information Sheet. You can still withdraw from the study at any time.

What if I have more questions or do not understand something?

If you have any queries, or would like more information about the study, please feel free to telephone the research team. Ms Linda Perkins-Porras can be contacted in the Department of Community Health Sciences, St. George's Hospital Medical School, Cranmer Terrace, London SW17 0RE (Tel 020 8725 5603) and Dr. Philip Strike at the Department of Epidemiology and Public Health, University College London, 1-19 Torrington Place, London, WC1E 6BT. Telephone 020 7679 1688. Since we cannot always be in our office, you might get an answer machine, but if you leave your name and telephone number, we will get back to you as soon as possible.

Appendix **xiv Session Instructions UCH / Southend patients**

The Stress and Coronary Disease Study
INSTRUCTIONS FOR PARTICIPANTS

- Please read the information sheet prior to the session.
- The evening before the session, please try to drink plenty of water.
- Please do **not** take part in strenuous exercise or drink alcohol from the evening before the session.
- We would like you to have breakfast (e.g. toast, cereal, fruit) the morning of the session, but please do not have a high-fat (i.e. fried foods) or high-protein (i.e. meat) breakfast.
- Please do not drink coffee, tea, coca-cola or other drinks containing caffeine on the morning of your visit. Please drink water or fruit juice instead.
- Please try and wear (or bring) comfortable clothing with loose sleeves/cuffs.
- Remember to keep all receipts for reimbursement of your travel expenses.
- If possible, we would be grateful if you could provide us with your birth weight when you attend the session.
- Please remember that we need to reschedule your appointment if you have a cold on the day of the session.

Please do not take Aspirin for 10 days before the study

Please remember to omit the following cardiac medication for 72 hours before your appointment - beta-blockers (e.g. atenolol), ACE inhibitors (e.g. ramipril) and statins (e.g. simvastatin). Omit other medications on the morning of the appointment.

Many thanks for your participation

Appendix xv Session Instructions St George's patients

The Stress and Coronary Disease Study

INSTRUCTIONS FOR PARTICIPANTS

- Please read the information sheet prior to the session.
- The evening before the session, please try to drink plenty of water.
- Please do **not** take part in strenuous exercise or drink alcohol from the evening before the session.
- We would like you to have breakfast (e.g. toast, cereal, fruit) the morning of the session, but please do not have a high-fat (i.e. fried foods) or high-protein (i.e. meat) breakfast.
- Please do not drink coffee, tea, coca-cola or other drinks containing caffeine on the morning of your visit. Please drink water or fruit juice instead.
- Please try and wear (or bring) comfortable clothing with loose sleeves/cuffs.
- Remember to keep all receipts for reimbursement of your travel expenses.
- If possible, we would be grateful if you could provide us with your birth weight when you attend the session.
- Please remember that we need to reschedule your appointment if you have a cold on the day of the session.

Please do not take Aspirin for 10 days before the study

Please remember to omit the following cardiac medication for 72 hours before your appointment - ACE inhibitors (e.g. ramipril) and statins (e.g. simvastatin). Continue with beta-blockers (e.g. atenolol) and other usual medication

Many thanks for your participation

Appendix xvi ROLE-PLAY SPEECH INSTRUCTIONS

In this task, I will present you with a hypothetical situation involving a real-life problem that could happen to anyone. In just a moment, I will read a description of this situation to you and then you will be given 2 minutes in which to prepare a response or story around the situation. You may look over what I'll read to you during your preparation time. Then, at the end of your preparation time, I will ask you to give your story for 3 minutes, talking at the video camera in front of you.

Try to imagine the emotions and feelings that you would experience if you were confronted by the situation that will be described. It's very important for our research that you not only try your hardest but that you also speak for the entire time. In addition, your task will be tape-recorded and later replayed by 3 of our laboratory staff and judged for "fluency, plausibility and confidence".

O.K. Here's your situation. (Read scenario to subject).

O.K. ANY QUESTIONS??

Fine. During your role-play speech, the measurements on your blood vessels will continue, so please keep as still as possible. Just try to conjure up the reactions you would experience in this stressful situation, and some heartfelt responses. You will now have two minutes to imagine yourself in this situation before you are asked to begin speaking. You may make notes if you wish. Once you have begun your speech, please try to continue without a break until you are told that the 3-minute period has come to an end. If necessary you can repeat things that you have already said.

Here's the written description of your situation – please make any notes on it if you wish to. I'll be back at the end of your 2-minute preparation time.

Appendix xvii **Participant code:** **Session no.:**

Role-Play Speech Scenario 1 – "Pickpocket"

Every day, we find ourselves having to deal with many difficult social situations. Imagine that you are in a busy department store and that you are trying to squeeze past a group of shoppers. You notice a purse on the floor. You bend down and pick it up and then open the purse to see if there is any identification inside. Suddenly, you feel a hand grab you on the shoulder and a stern voice says "Ok, come with me, I saw you steal that purse". As you are being led to the manager's office you realise that the security guard believes you are a pickpocket. The police are called immediately, and it is up to you to defend yourself.

What we want you to do in this task is to speak as if you were trying to defend yourself to the police. Remember that if you do not give a clear account of what happened, the police are likely to prosecute you. If the case goes any further, you may be answering questions before a judge. Try to conjure up the feelings you would experience in this situation, and think quickly about how best to defend yourself.

Here are some things you might do. Firstly, describe what actually happened and try to give reasons to the police why you wouldn't have stolen the purse. Secondly, think about how you would feel about the security guard for making this serious mistake about you. Perhaps you would criticise the department store for employing incompetent and trigger-happy guards. Thirdly, think of ways that you could convince the police that you are not the sort of person who would commit this crime.

xviii Consent form

Royal Free and University College Medical School

UNIVERSITY COLLEGE LONDON

DEPARTMENT OF EPIDEMIOLOGY AND PUBLIC HEALTH

Gower Street Campus
1-19 Torrington Place
London WC1E 6BT

Telephone 44 (0) 020 7679 2000

Study Number:
Patient Identification Number for this trial:

CONSENT FORM (Confidential)

Title of project: **A Study of Stress and Coronary Artery Disease – Trigger Study**

Name of Researcher: Professor Andrew Steptoe, Dr. Lena Brydon, Dr. Sue Edwards, Dr. Philip Strike
Any questions to Dr. Philip Strike, Department of Epidemiology and Public Health, University College London, 1-19 Torrington Place, London, WC1E 6BT. Telephone 020 7679 1804

Please initial box

1. I confirm that I have read and understood the information sheet for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that sections of any of my medical notes may be looked at by responsible individuals from (company name) or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐
4. I agree to take part in the above study. ☐

Name of patient	Date	Signature

Name of Person taking consent (if different from researcher)	Date	Signature
Researcher	Date	Signature

Appendix xix Trigger Laboratory protocol

TRIGGER STUDY PROTOCOL

Participant ID			
Date		Date of Birth	
Start time		Time of Awakening	

Cycling Lab (0900h):

- Information sheet and consent form
- Confirm health status detailed in information sheet
- Check instructions were followed: medication (48-hour and 10-day)/ alcohol / exercise / caffeine
- Time and content of last meal

  .....
- How did they travel to the session? (did anything unusual happen?)

  .....
- Brief verbal explanation of study
- First **SALIVA (1)** sample (2 min chewing gently) STOP WATCH 2 MIN

Physical Measures			
Height	m	Weight	kg
Hip measure	cm	Waist measure	cm
Bodystat measurement (recover data after session)			

- TOILET

Stress Lab (0925h): *(check room temperature is 22° and prepare heat pad)*

- **(Initialise Portapres: enter physical data and set cuffs to 1-min switching interval)**
- Needle insertion and heat pad
- Attach Portapres cuffs (middle and ring) and height line (explain camera and uncrossed legs)

- Switch Portapres (PP) on (START/STOP button) to ensure both cuffs work OK
- Casual BP SBP _____ DBP _____ HR _____ (habituation)
- PP off (START/STOP button), **change to 30-min cuff interval** and leave in ready mode

Rest Period (0945h) **START CLOCK**

- **At 10 min:** PP on (START/STOP) (remember to monitor times of cuff switch)

ENSURE PP START/STOP BUTTON NOT PRESSED DURING THE SESSION

ENSURE DISPLAY READS BETWEEN 30/06 AND 30/28 BEFORE RECORDING EVENTS

- **At 25 min:**

  © **Calibration off** © press PP **event** button

- **At 30 min:**

  © Press PP **event** button © **calibration on** *(at 40 min, 1025h cuff switch)*

  © Rest Questionnaire

  © Casual BP SBP _____ DBP _____ HR _____

  wait 1 minute, sitting quietly

  © Casual BP SBP _____ DBP _____ HR _____

  © **SALIVA (2)** STOP WATCH 2 MIN and **BLOOD (1)** Start time ..... Stop time .....

Stress Tasks (1030h) *(change heat pad, if necessary)*

STROOP

- Give written instructions. *While they are reading instructions, set up Stroop.*
- Talk the participant through the practice
- Let the participant have a go at the practice until they have the idea (within reason)
- **Calibration off** © start Stroop (F3 return) © press PP **event** button
- At the end of the task, press PP **event** button © **calibration on** *(3 enter, 3 enter on computer)*
- Task impact questionnaire

SPEECH

- Explain the task to the participant. Then hand them the written instructions and say they will have 2 min to prepare
- **Calibration off** © start task (=*2min preparation time and 3min speech*) © press PP **event** button
- **Start stopwatch and time 2 min preparation. Then instruct to start speech and time 3 min.**
- At end of 3 minutes speech say **you can stop now,** press PP **event** button © **calibration on**

Task impact questionnaire

Recovery period (1050 – 1400h) START CLOCK TIME NOW:

(cuff switch at 1055h)

Immediately post-task:

- Casual BP SBP _____ DBP _____ HR _____
- **SALIVA (3)** STOP WATCH 2 MIN and **BLOOD (2)** Start time ..... Stop time .....

change heat pad

- Check calibration is on
- **At 15 min: SALIVA (4)** STOP WATCH 2 MIN
- **At 25 min:**

  ©**Calibration off** © press PP **event** button
- **At 30 min:**

  © Press PP **event** button *(at 35 min: 1125h cuff switch)*

  © **Calibration on**

  © Recovery Questionnaire (1)

  © **SALIVA (5)** STOP WATCH 2 MIN and **BLOOD (3)** Start time ..... Stop time .....

(should finish by 36 min)

(Change heat pad)

** 30 min for 1st questionnaire **

(at 1h5m: 1155h cuff switch)

- **At 1h10 min:**

  ©**Calibration off** © press PP **event** button

- **At 1h15 min:**

  © Press PP **event** button

  © **Calibration on**

  © Recovery Questionnaire (2)

  © **SALIVA (6)** STOP WATCH 2 MIN and **BLOOD (4)** Start time ..... Stop time .....

  (should finish by 1h21)

(at 1h 35min: 1225h cuff switch) *(Change heat pad)*

** 30 min for 2nd questionnaire **

- **At 1h 55m:**

  ©**Calibration off** © press PP **event** button

- **At 2h:** *(at 2h5m: 1255h cuff switch)*

  © Press PP **event** button

  © Turn Portapres off (START/STOP button)

  © Recovery Questionnaire (3)

  © **SALIVA (7)** STOP WATCH 2 MIN and **BLOOD (5)** Start time ..... Stop time .....

  (should finish by 2h6m)

- Needle out
- Take out PP air hose and cable, remove cuffs and height line, turn off at wall.

COMMENTS ABOUT SESSION (Note anything that went wrong including button pressed out of place or missed):